European Union Risk Management Plan
STELARA® (ustekinumab)

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QPPV Name(s):	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The Marketing Authorization Holder (MAH) QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	31.2
Rationale for submitting an updated RMP	Revision of milestones for the end of data collection and the final study report for the CNTO1275ISD3001 (UNITED) LTE per EMA request (Procedure No. EMEA/H/C/000958/II/0108).
Summary of significant changes in this RMP	Updated milestones for the end of data collection and the final study report for the CNTO1275ISD3001 (UNITED) LTE in the following sections of the RMP: • Part III: Pharmacovigilance Plan, Sections III.2 (Additional Pharmacovigilance Activities) and III.3 (Summary Table of Additional Pharmacovigilance Activities) • Part V: Risk Minimization Measures, Section V.3 (Summary of Risk Minimization Measures and Pharmacovigilance Activities) • Annex 2: Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program, Table 1 (Planned and Ongoing Studies)

Other RMP Versions Under Evaluation:

RMP Version Number	**Submitted on**	**Procedure Number**
29.1	02 July 2024	EMEA/H/C/000958/II/0108
31.1	28 November 2024	EMEA/H/C/000958/II/0108

Details of the Currently Approved RMP:

Version number of last agreed RMP:	Version 30.1
Approved within Procedure	EMEA/H/C/000958/II/0104
Date of approval (Competent authority opinion date)	05 September 2024

TABLE OF CONTENTS

PART I: PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	Ustekinumab
Pharmacotherapeutic group(s) (ATC Code)	L04AC05
Marketing Authorization Holder	Janssen-Cilag International, NV
Medicinal products to which the RMP refers	Ustekinumab (STELARA®)
Invented name(s) in the European Economic Area (EEA)	STELARA®
Marketing authorization procedure	Centralized
Brief description of the product Chemical class Summary of mode of action Important information about its composition	Ustekinumab is a fully human IgG1κ monoclonal antibody (mAb) with a molecular weight of approximately 148,600 Daltons. Ustekinumab binds human and primate interleukin (IL)-12/23p40 protein with specificity. Ustekinumab prevents the binding of IL-12 or IL-23 to the cell surface IL-12Rβ1 receptor, and thereby blocks receptor signaling. In this manner, ustekinumab inhibits the biological activity of IL-12 and IL-23 in all in vitro assays examined.
Reference to the Product Information	Mod1.3.1/Summary of Product Characteristics (SmPC), Labelling and Package Leaflet (PL)
Indication(s) in the EEA	Current: <u>Plaque psoriasis</u> STELARA 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 cyclosporin, methotrexate (MTX) or psoralen and ultraviolet A (PUVA). <u>Pediatric plaque psoriasis</u> STELARA 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. <u>Psoriatic arthritis</u> STELARA, 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. <u>Adult Crohn's disease</u> STELARA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNFα) antagonist.

	Ulcerative colitis STELARA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic. Pediatric Crohn's disease STELARA is indicated for the treatment of moderately to severely active CD in pediatric patients weighing 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:

Plaque psoriasis

The recommended posology of STELARA is an initial dose of 45 mg administered subcutaneously, followed by a 45-mg dose 4 weeks later, 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, then every 12 weeks thereafter.

Psoriatic arthritis

The recommended posology of STELARA 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.

Pediatric plaque psoriasis (6 years and older)

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

Adult Crohn's disease and ulcerative colitis

STELARA 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 STELARA 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 STELARA solution for injection (vial) and solution for injection in pre-filled syringe SmPC or the pre-filled pen SmPC.

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

STELARA 130 mg concentrate for solution for infusion

STELARA 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 STELARA 130 mg as specified in the table below.

Body weight of patient at the time of dosing	Recommended dose[a]	Number of 130 mg STELARA vials
≥ 40 kg to ≤ 55 kg	260 mg	2
> 55 kg to ≤ 85 kg	390 mg	3
> 85 kg	520 mg	4

[a]: Approximately 6 mg/kg

STELARA 45 mg solution for injection/STELARA 45 mg solution for injection in pre-filled syringe/STELARA 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 STELARA solution for injection (vial) and solution for injection in pre-filled syringe SmPC.	
	Proposed: Not applicable.	
Pharmaceutical form(s) and strengths	Current: <u>For SC use</u> Solution for injection: 45 mg/0.5 mL. Solution for injection in pre-filled syringe: 45 mg/0.5 mL and 90 mg/1 mL. Solution for injection in pre-filled pen (for adult use): 45 mg/0.5 mL and 90 mg/1 mL. <u>For IV use</u> Concentrate for solution for infusion: 130 mg/26 mL (5 mg/mL).	
	Proposed: Not applicable.	
Is/will the product subject of additional monitoring in the EU?	☐ **Yes**	☑ **No**

PART II: SAFETY SPECIFICATION

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

Indication: Adult Psoriasis

Incidence:

Data on the incidence of specific forms of psoriasis are limited.

Globally, the incidence of psoriasis in adults 20 years of age and older has been estimated to be 72.64 per 100,000 person years (PY) (69.68-75.52 lower and upper limits) for 2019 (Global Health Data Exchange 2021). A systematic review reported the incidence of psoriasis in adults ranged from 30.3 per 100,000 PY in Taiwan to 321.0 per 100,000 PY in Italy (Parisi 2020). A nationwide study in Denmark that followed the entire adult population from 2003 to 2012 reported an incidence of 151.22 per 100,000 PY for 2012 (Egeberg 2017a). The incidence of psoriasis in the United Kingdom (UK) was reported as 129 per 100,000 PY between 1999 and 2013 using Clinical Practice Research Datalink (CPRD) data (Springate 2017).

Two studies from the United States (US) gave estimates for the incidence of psoriasis:

- Annual incidence of 78.9 per 100,000 PY (95% confidence interval [CI] 75.0 to 82.9) in both sexes between 1970 and 2000 (Icen 2009)
- 82 per 100,000 PY (95% CI 77 to 89) in women from 1991 to 2005 (Setty 2007).

Prevalence:

According to the Global Burden of Disease study, the prevalence of psoriasis in adults 20 years of age and older was 693.95 per 100,000 (669.29-717.64 lower and upper limits) in 2019 (Global Health Data Exchange 2021). A systematic review of worldwide epidemiology reported that the regional prevalence of psoriasis in adults ranged from 0.14% in east Asia to 1.99% in Australasia. For specific countries, the highest estimates of prevalence were in Australia (1.88%, 95% CI 0.59 to 6.10), Norway (1.86%, 95% CI 0.94 to 3.97), Israel (1.81%, 95% CI 0.83 to 4.44), and Denmark (1.79%, 95% CI 0.91 to 3.61). The lowest prevalence estimate was in Taiwan (0.05%; 95% CI 0.02 to 0.16) (Parisi 2020).

Using data from the CPRD, prevalence estimates in the UK were 2.8% between 1999 and 2013 (Springate 2017). Among 9,035 patients with psoriasis in a UK medical records study, 51.8%, 35.8%, and 12.4% had mild, moderate, or severe disease, respectively, based on body surface area (BSA) criteria (Yeung 2013).

Prevalence estimates of psoriasis in the US range from 2.2% to 3.15% (Parisi 2013). Findings from a nationally representative sample survey from the US which gathered data from 2009 to 2010 reported the prevalence of psoriasis among adults aged 20 years and older as 3.2% (95% CI 2.6 to 3.7). Consistent results reporting the overall prevalence of psoriasis as 3.1% were published in another national US study (Helmick 2014). A total of 7.2 million adults in the US had psoriasis in 2010, and an estimated 7.4 million adults in the US were affected in 2013 (Rachakonda 2014).

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 (Parisi 2013). 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. Parisi (2013) found 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.

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 (Rachakonda 2014).

A weak correlation between geographic latitude and psoriasis prevalence has been reported, with psoriasis appearing to occur most frequently in northern European countries and least frequently in eastern Asia (WHO 2016).

Risk Factors

One risk factor for psoriasis is family history, with approximately 40% of people with psoriasis having a family member with the disease. Genetics may also play a key role in psoriasis, with several studies finding a strong association between psoriasis and human leukocyte antigen (HLA) class I genes (Eder 2015).

Viral or bacterial infections are also a risk factor for psoriasis. For example, people with human immunodeficiency virus (HIV), as well as children and young adults with recurring infections (particularly strep throat), are more likely to develop psoriasis compared with people with healthy immune systems. Other identified risk factors for psoriasis include high stress levels, and smoking tobacco (Mayo Clinic 2020d).

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 (Mayo Clinic 2020c):

- 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 (ie, 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, MTX, hydroxyurea, immunomodulator drugs (including apremilast, azathioprine [AZA], cyclosporine, and leflunomide), biologics (including adalimumab, etanercept, golimumab, guselkumab, infliximab, ixekizumab, and secukinumab), thioguanine, brodalumab, and certolizumab pegol.

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

Because observational studies generally include a treated population, it is difficult to describe the course of the indicated condition in the untreated population and to distinguish the effects of treatment from the natural history of the disease. This applies to all indications discussed in this RMP.

The extent and duration of psoriasis is highly variable. Plaque psoriasis is the most common type, occurring in more than 80% of cases (Lebwohl 2003). Acute flares or relapses of plaque psoriasis may also evolve into more severe disease, such as pustular or erythrodermic psoriasis, with or without treatment. Each of these occur in <3% of patients (Lebwohl 2003). 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 (Yeung 2013).

Patients with psoriasis may experience significant physical discomfort and some disability. Itching and pain can interfere with basic functions (NIAMSb 2017). 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 (Yeung 2013).

Mortality

Dhana (2019) conducted 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% CI 1.14 to 1.28) in psoriasis, 1.13 (95% CI 1.09 to 1.16) in mild psoriasis, and 1.52 (95% CI 1.35 to 1.71) in severe psoriasis. The pooled relative risk was 1.15 (95% CI 1.09 to 1.21) for cardiovascular mortality, 2.16 (95% CI 1.37 to 3.40) for kidney disease, and 2.31 (95% CI 1.61 to 3.31) for liver disease (Dhana 2019).

A nationwide Danish population-based cohort with a total of 5,458,627 adult patients included 94,069 with mild psoriasis and 28,253 with severe psoriasis. A total of 10,916 and 3,699 deaths were recorded in patients with mild and severe psoriasis, respectively. Overall death rates were 13.8, 17.0, and 25.4 per 1,000 PY for the general population, patients with mild psoriasis, and patients with severe psoriasis, respectively (Salahadeen 2015).

Important Co-morbidities:

Co-morbidities that occur in adult patients with psoriasis include psoriatic arthritis (PsA); inflammatory bowel disease (IBD); non-melanoma skin cancer (NMSC), probably due to light therapy for psoriasis; depression; uveitis; obesity; metabolic syndrome (or components thereof); cardiovascular (CV) disease; type 2 diabetes, and immune-mediated disorders (Pouplard 2013; Mayo Clinic 2020d).

Indication: Pediatric Psoriasis

Incidence:

Globally, the incidence of psoriasis in the population less than 20 years old in 2019 was 33.95 per 100,000 per PY (31.85-36.19 lower and upper limits) (Global Health Data Exchange 2021).

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% CI 36.6 to 45.1) from 1970 to 1999 (Tollefson 2010). When the psoriasis diagnosis was restricted to dermatologist-confirmed subjects in the medical record, the incidence was 33.2 per 100,000 (95% CI 29.3 to 37.0). Incidence of psoriasis in children increased significantly over time from 29.6 per 100,000 (1970-1974) to 62.7 per 100,000 (1995-1999; p<001). In Italy for the year 2012, the incidence of psoriasis in children up to 14 years old was reported to be 0.57 per 1000 person years (Cantarutti 2015).

Up to 75% of children with psoriasis have plaque psoriasis (Tollefson 2014).

Prevalence:

Globally, the prevalence of psoriasis in the population less than 20 years old in 2019 was 194.25 per 100,000 population (183.02-207.19 lower and upper limits) (Global Health Data Exchange 2021). 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) (Burden-Teh 2016). A claims-based study conducted in the US estimated the annual prevalence of psoriasis in 2015 in patients less than 18 years of age as 128 cases per 100,000 individuals (95% CI 124 to 131) (Paller 2018).

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

The median age of onset of childhood psoriasis has been reported to be between 7 and 10 years (Eichenfield 2018). 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 (see table below). 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 (Parisi 2013). In a German health insurance database study, the prevalence of psoriasis in children and adolescents was 0.4% overall, ranging from 0.1% at 1 year of age to 0.8% at 18 years of age in 2007 (Matusiewicz 2014).

	Annual Incidence per 100,000 Pediatric Population		
Age group	**Male**	**Female**	**Total**
0-3	13.7	13.2	13.5
4-7	44.1	40.2	42.2
8-10	33.2	55.7	44.0
11-13	54.6	49.6	52.2
14-17	44.7	61.9	53.1
Total	37.9	43.9	40.8

Source: Tollefson 2010

In the US, a claims-based analysis reported that 55.7% of patients with psoriasis under the age of 18 years were between 12 and 17 years old, 40.0% were 4 to 11 years old, and 4.3% were 3 years old or younger in 2015 (Paller 2018). In a large German health insurance study of juvenile psoriasis, the prevalence of psoriasis showed an increasing trend with increasing age in 2007 is shown below (Matusiewicz 2014).

Age (years)	Prevalence	Age (years)	Prevalence	Age (years)	Prevalence
<1	0.03%	7	0.23%	14	0.53%
1	0.09%	8	0.34%	15	0.60%
2	0.10%	9	0.33%	16	0.63%
3	0.10%	10	0.36%	17	0.76%
4	0.17%	11	0.38%	18	0.82%
5	0.15%	12	0.45%		
6	0.20%	13	0.52%		

Source: Matusiewicz 2014

White children are the most affected compared with other ethnicities, and they have an earlier mean age of onset. Approximately 0.71% of European children are affected; in Asia, psoriasis is almost absent (Relvas 2017).

Risk Factors

Many of the risk factors for psoriasis in adults also apply to the pediatric population. Specifically, genetics play a key role in pediatric psoriasis, with many children with psoriasis having a first-degree relative with the disease (Tollefson 2014). 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 (Ozden 2011). Other identified risk factors include infection, stress (usually emotional or psychological) and a history of trauma (Burden-Teh 2016). Obesity was also cited as a risk factor, in agreement with data published by Ozden in 2011.

The Main Existing Treatment Options:

Tollefson (2014) summarized psoriasis treatments used in the pediatric population. Topical skin-directed treatment is sufficient for most children, especially those with mild to moderate psoriasis. Occlusive ointments are often more effective than creams or lotions but may not be appealing to the adolescent population.

Topical steroids are the most frequently prescribed medication used as first-line treatment of childhood psoriasis. Other topical treatments include vitamin D analogues (calcipotriene and calcitriol), tars (crude coal tar and liquid carbonis detergents), anthralin (dithranol), topical calcineurin inhibitors (tacrolimus and pimecrolimus), and tazarotene. Keratolytics (salicylic acid, lactic acid, and urea) can be used as adjunctive treatments. Antistreptococcal antibiotics may be given to patients with active streptococcal infection. Children with severe or refractory disease may require phototherapy and/or systemic treatment with medications such as MTX, cyclosporin, oral retinoids, or biologics.

Often, combinations of treatments are used to increase efficacy while limiting toxicity.

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 (Bronckers 2015).

Patients with childhood-onset psoriasis are more likely to have significant disease and flares compared with those with adult-onset psoriasis (Burden-Teh 2016).

Mortality

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 metabolic syndrome (or components thereof), obesity, diabetes mellitus, and CD (Augustin 2010).

Indication: Psoriatic Arthritis

Incidence:

A meta-analysis of 28 population studies reported a pooled incidence of PsA of 8.3 per 100,000 PY (95% CI 4.1 to 16.7). Interstudy heterogeneity was high, with incidence ranging from 3.0 to 41.3 cases per 100,000 PY (Scotti 2018). In Denmark, the incidence of PsA for 2011 was reported at 19.8 per 100,000 PY (Egeberg 2017b). A meta-analysis of 10 studies of psoriasis patients reported PsA incidence rates ranging from 0.27 per 100 PY to 2.7 per 100 PY (Alinaghi 2019).

Prevalence:

Scotti (2018) reported a pooled prevalence of PsA of 133 per 100,000 population, ranging from 20 to 670 cases per 100,000 population. 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% CI 0.185 to 0.193) (Ogdie 2013). Interstudy heterogeneity was high, with some of the differences explained by PsA detection criteria. Other studies reported that 11% and 42% of patients with plaque psoriasis also experience PsA (Gelfand 2005; Gladman 2005). A meta-analysis of 266 studies reported a pooled prevalence of 19.7% (95% CI 18.5 to 20.9) among psoriasis patients (Alinaghi 2019).

Demographics of the Population in the PsA 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. The average age of onset of PsA is 36 to 40 years of age, although the actual male:female ratio may vary depending upon the subset in question (Gladman 2009a). Prevalence by age and sex as reported in the study based on the THIN database conducted by Ogdie (2013) is shown in the following table.

Age (years)	Men		Women		All	
	PsA (n)	Prevalence (%)	PsA (n)	Prevalence (%)	PsA (n)	Prevalence (%)
18-29	316	0.05	353	0.05	669	0.05
30-39	916	0.17	819	0.16	1,735	0.16
40-49	1,157	0.29	952	0.26	2,109	0.28
50-59	1,115	0.36	1,092	0.36	2,207	0.36
60-69	675	0.31	733	0.32	1,408	0.31
70-80	334	0.23	380	0.20	714	0.21
80-90	75	0.12	128	0.10	203	0.11
All	**4,591**	**0.20**	**4,461**	**0.18**	**9,045**	**0.19**

Source: Ogdie 2013

Risk Factors

Having psoriasis is the single greatest risk factor for developing PsA; individuals with lesions on nails are especially at risk (Mayo Clinic 2021a). An infectious agent may also trigger the

psoriatic process. The immunological response observed in patients with psoriasis or PsA may be the result of mimicry between streptococcal antigens and epidermal autoantigens. The exacerbation of psoriasis and PsA seen in the context of acquired immunodeficiency virus infections suggests that HIV may play a role (Gladman 2009a).

Psoriatic arthritis most often develops in adults between the ages of 30 and 50 years. Studies have suggested a high risk for PsA among first-degree relatives (Mayo Clinic 2021a). Approximately 20% to 30% of psoriasis patients eventually develop PsA (Ocampo 2019). There may be a genetic component, particularly with HLA class 1 alleles at the B and C loci. In addition to being associated with presence of the disease, HLA antigens have been identified as prognostic markers for the progression of clinical damage in PsA (Gladman 2009a).

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 anti-inflammatory drugs (NSAIDs). Traditional disease-modifying anti rheumatic drugs (DMARDs) such as MTX, sulfasalazine, and leflunomide are used when poor prognostic indicators are present. Finally, biologics such as TNFα inhibitor and anti-IL-17a therapies should be considered when inflammation persists despite traditional treatment. Intra-articular and entheseal injections can also be employed (Day 2012a).

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

Approximately 30% of patients with psoriasis develop PsA (Gladman 2016); see also the incidence and prevalence data above regarding PsA.

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 (Gladman 2005). As the disease progresses, 20% of patients develop a very destructive and disabling form of arthritis, and 47% sustain erosive changes after 2 years of disease (Gladman 2009b). In patients followed for more than 10 years, 55% had 5 or more deformed joints (Gladman 2005).

<u>Mortality</u>

In a study that identified 8,706 patients from THIN, the overall mortality rate of PsA patients was 10.37 deaths per 1,000 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 (Ogdie 2014; Ogdie 2017). A Canadian study of 1,490 PsA patients followed for 15,060 PY reported an overall standardized mortality ratio (SMR) of 0.92 (95% CI 0.81 to 1.05) in reference to the general population of Ontario. In this study, major causes of death were malignant neoplasms, acute myocardial infarction, and pneumonia (Elalouf 2020). In a US population-based study conducted over a 30-year period, the survival of PsA subjects did not differ from that of the general population (Wilson 2009).

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 (Haddad 2017; Ocampo 2019).

Indication: Adult Crohn's Disease

Incidence:

In a systematic review of the worldwide incidence of CD from 1990 to 2016, the annual incidence varied by geographic region, with estimates as high as 15.4 per 100,000 PY in Europe, 0.06 to 8.4 per 100,000 PY in Asia, 6.3 to 23.82 per 100,000 PY in North America, and 0.0 to 3.5 per 100,000 PY in South America (Ng 2018).

For specific regions of Europe, the incidence for 1990 to 2016 ranged from 0.4 to 14.6 per 100,000 PY in Eastern Europe, 0.0 to 11.4 per 100,000 PY in Northern Europe, 0.95 to 15.4 per 100,000 PY in Southern Europe, and 1.85 to 10.5 per 100,000 PY in Western Europe (Ng 2018). A large number of studies have reported on incidence of CD in specific countries. One study reported the incidence in Canada and the UK, respectively, to be 20.2 and 10.6 per 100,000 persons (Molodecky 2012). Another study reported that the incidence of CD in Europe ranges from 0 to 11.5 per 100,000 PY (Burisch 2015). A study in Finland between 2000 and 2007 revealed an overall incidence of 9.2 per 100,000 population (Hovde 2012; Jussila 2012). A study of IBD patients in the EPIMAD registry in France between 1988 and 2007 found that CD incidence increased from 5.2 per 100,000 population (1988-1990) to a peak at 7.1 per 100,000 population (1997-1999) before stabilizing at 6.7 per 100,000 population from 2006 to 2007 (Chouraki 2011). A study conducted in Denmark estimated an incidence of CD from 1980 to 2013 as 9.1 (95% CI 8.7 to 9.5) per 100,000 population (Lophaven 2017). In the Netherlands, the incidence of CD was reported as 10.5 per 100,000 PY (de Groof 2016).

Generally, the incidence of CD is increasing in the Western world, including North America, Europe, Australia, and New Zealand (Aniwan 2017).

Prevalence:

In a literature review that covered 1990 to 2016, estimates of the prevalence of CD ranged from 1.51 to 322 per 100,000 population in Europe, 1.05 to 53.1 per 100,000 population in Asia, 96.3 to 318.5 per 100,000 population in North America, and 0.9 to 41.4 per 100,000 population in South America (Ng 2018).

For specific regions of Europe for the period 1990 to 2016, prevalence estimates ranged from 1.51 to 200 per 100,000 population in Eastern Europe, 24.0 to 262.2 per 100,000 population in Northern Europe, 4.5 to 137.17 per 100,000 population in Southern Europe, and 28.2 to 322.0 per 100,000 population in Western Europe (Ng 2018). Another study reported prevalence in Europe ranging from 1.5 to 213 per 100,000 population (Burisch 2015). In the Netherlands, the prevalence of CD has been reported as 171.8 per 100,000 population from 2004 to 2010 (de Groof 2016). More recently, a Spanish study reported a prevalence of 191.4 per 100,000 population in 2016 (Brunet 2018). In the US, the prevalence of CD in adults (age over 17 years) was reported as 197.7 per 100,000 population (95% CI 195.8 to 199.6) (Ye 2020).

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 (Sonnenberg 2010). The median age of onset is 30 years (Feuerstein 2017).

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 (Shah 2018). 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 (Hovde 2012). The aforementioned study by Chouraki (2011) in France also showed a predominance of females with CD (56%) between 1988 and 2007. A regional study conducted in Spain from 2007 to 2008 reported the incidence for CD as 5.1 per 100,000 population for both males and females (Cueto Torreblanca 2017).

The frequency of CD varies among ethnic groups, with increased prevalence reported for Ashkenazi Jews compared with the non-Jewish population living in the same geographic area. A review regarding data from a southern California health management organization reported that the prevalence of CD among blacks was approximately two-thirds that of whites, although the rates of hospitalization for CD were similar. Hospitalizations for CD in Asian-Americans are uncommon (Loftus 2004). In addition, Hispanics in the US are less prone to develop IBD than the non-Hispanic population (Hovde 2012).

Occurrence of CD seems to vary according to geographical location. Crohn's disease is more common in the industrialized world compared with nonindustrialized countries (Feuerstein 2017). Moreover, a north-south axis has been found in both Europe and the US, with higher incidence and prevalence in the northern regions (Hovde 2012). Another review suggested a northwest/southeast gradient in IBD incidence (Burisch 2013).

Risk Factors

Risk factors for CD include age younger than 30 years, being white or of Ashkenazi Jewish descent, having a close relative with the disease, and living in urban or industrialized areas. A low-fiber, high-fat diet; use of certain medications (such as antibiotics, NSAIDs, and oral contraceptives) (Aniwan 2017), and having had an appendectomy or tonsillectomy (Piovani 2019) are also risk factors for CD. The most important controllable risk factor is cigarette smoking (Mayo Clinic 2020b).

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.

- 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 (Mayo Clinic 2020a). Rates of bowel resection procedures range from 12% within 1 year of diagnosis in Denmark to 35% within 5 years in the UK (Hovde 2012).

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

Crohn's disease begins gradually, becoming worse over time, with a naturally recurring and remitting disease course (NIDDK 2017; Lashner 2013). 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 (NIDDK 2017). Additionally, approximately 25% to 46% of patients with CD experience extra-intestinal manifestations (Hovde 2012). One study conducted in Hungary reported that the probability of developing more complicated disease in adult-onset CD patients was 12.1%, 26.4%, and 37.5% after 1, 5, and 10 years of follow-up, respectively (Lovasz 2013). Similarly, 27.1% of CD patients in Europe develop stricturing disease and 29.4% develop penetrating disease within 10 years of diagnosis (Burisch 2013).

Mortality

A meta-analysis reported an increased mortality ratio in patients with CD (SMR=1.39, 95% CI 1.30 to 1.50) (Burisch 2013) compared with the general population. According to a review, mortality is up to 40% higher in European patients with CD compared with the general population (Burisch 2013). A Spanish study reported a mortality rate of 17.0 per 100,000 population in 2016 (Brunet 2018).

In a study from Ireland that included 1,101 patients less than 65 years of age with CD, a total of 29 patients died before the age of 65 years during a mean follow-up of 8.9 years (O'Toole 2014). Data based on a prospective study that included 5,315 patients with CD (diagnosed from either 1987-1993 or 2000-2007 and followed through the end of 2010) reported a 33% increased overall mortality in these patients (SMR=1.33, 95% CI 1.21 to 1.46) (Jussila 2014). A Swedish study reported an incidence of 14.8 per 1,000 PY (95% CI 14.4 to 15.2) and a hazard ratio (HR) of 1.6 (95% CI 1.6 to 1.7) for all-cause mortality in CD for the years 1964-2014 (Olén 2020).

A study in southeastern Norway followed all patients diagnosed with CD between 1990 and 1993 for 20 years. Hovde (2013) found no difference between CD patients and controls in overall mortality (HR=1.35, 95% CI 0.94 to 1.94; p=0.10). In total, 13.9% of patients in the CD group died compared with 12.7% of patients in the control group (p=0.578). There were no marked differences in deaths from gastrointestinal cancer, other cancers, or CV disease in

the CD group compared with controls. No explanation for the possible difference from other studies was described (Hovde 2013).

Important Co-morbidities:

Co-morbidities that occur in CD patients include small bowel or colorectal cancer; uveitis; episcleritis; arthritis; hepatobiliary disorders; nephrolithiasis; fat malabsorption; pancreatic disease; obesity; CV conditions, including venous thromboembolism (VTE) and atherosclerosis; depression; anxiety; and bipolar disorder (Román 2011; Burisch 2013; Cury 2013; Crohn's and Colitis Foundation 2012; Bernstein 2019).

Indication: Ulcerative Colitis

Incidence:

In a systematic review of the worldwide incidence of UC from 1990 to 2016, the annual incidence of UC varied by geographic region, with estimates ranging from 0.97 to 57.9 per 100,000 PY in Europe, 8.8 to 23.14 per 100,000 PY in North America, 0.15 to 6.5 per 100,000 PY in Asia, and 0.19 to 6.76 per 100,000 PY in South America (Ng 2018).

For specific regions of Europe for the period 1990 to 2016, reported incidence ranged from 0.97 to 11.9 per 100,000 PY in Eastern Europe, 1.7 to 57.9 per 100,000 PY in Northern Europe, 3.3 to 11.47 per 100,000 PY in Southern Europe, and 1.9 to 17.2 per 100,000 PY in Western Europe (Ng 2018). A national study conducted in Denmark, which included all ages, estimated the incidence of UC in 2013 to be 18.6 (95% CI 18.0 to 19.2) per 100,000 population (Lophaven 2017). In the Netherlands, the incidence has been reported at 17.2 per 100,000 PY (de Groof 2016). In a study to evaluate the incidence of UC in the Uppsala Region of Sweden, all new UC patients were prospectively registered from 2005 to 2006 and from 2007 to 2009. The mean overall incidence for the time period was 20.0 (95% CI 16.1 to 23.9) per 100,000 population (Sjöberg 2013). Another regional Swedish study reported an incidence of 18.1 per 100,000 population in 2010 (Eriksson 2017). A systematic review of studies conducted in Latin America reported the incidence of UC to range between 0.04 and 8.00 per 100,000 PY (Kotze 2020).

Prevalence:

In a systematic review of the worldwide prevalence of UC from 1990 to 2016, the prevalence of UC varied by geographic region, with estimates ranging from 2.42 to 505.0 per 100,000 population in Europe, 139.8 to 286.3 per 100,000 population in North America, 4.59 to 106.2 per 100,000 population in Asia, and 4.7 to 44.3 per 100,000 population in South America (Ng 2018). A systematic review of studies conducted in Latin America reported the prevalence of UC to range between 0.23 and 76.1 per 100,000 population (Kotze 2020).

For specific regions of Europe for the period 1990 to 2016, prevalence estimates ranged from 2.42 to 340.0 per 100,000 population in Eastern Europe, 90.8 to 505.0 per 100,000 population in Northern Europe, 14.5 to 133.9 per 100,000 population in Southern Europe, and 43.1 to 412.0 per 100,000 population in Western Europe (Ng 2018).

In the Netherlands, the point prevalence of UC has been reported as 225.6 per 100,000 population for 2004 to 2010 (de Groof 2016). Molodecky (2012) reported prevalence ranging from 4.9 to 505 per 100,000 population in Europe and 37.5 to 248.6 per 100,000 population in North America. Prevalence was highest in Norway (505 per 100,000 population) and Canada (248 per 100,000 population). Eriksson (2017) reported the point prevalence for 2010 to be 474 (95% CI 444 to 506) per 100,000 population in Sweden. A Spanish study reported a prevalence of 353.9 per 100,000 population in 2016 (Brunet 2018). In the US, the prevalence of UC in adults (age over 17 years) was reported as 181.1 per 100,000 population (95% CI 179.3 to 182.9) (Ye 2020).

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

The incidence of UC has a bimodal age distribution, with a first peak in the second or third decades of life and a second peak between the ages of 50 and 80 years (Gajendran 2019). A regional study conducted in Spain reported the incidence rate for UC in women as 2.7 per 100,000 population and 5.1 per 100,000 population in men for 2007 to 2008 (Cueto Torreblanca 2017). A pooled analysis of studies conducted in Europe, North America, Australia, and New Zealand reported that incidence rates of UC were similar in men and women until the 40- to 44-year age group. After the age of 45 years, women had a lower risk of developing UC compared to men until the 70- to 74-year age group (Shah 2018).

Risk Factors

Risk factors for UC include age (disease onset is usually <30 years), being white or of Ashkenazi Jewish descent, and a family history of the disease (Mayo Clinic 2021c). Smoking and a high-fat diet may also increase the chance of developing UC. There is also evidence that use of NSAIDs, oral contraceptives, and antibiotics may be associated with an increased risk of UC (Roda 2020).

The Main Existing Treatment Options:

The goal of medical treatment for UC is to reduce the inflammation that triggers signs and symptoms of the disease. In the best cases, this may lead not only to symptom relief, but also to long-term remission. Drugs used for the pharmacologic management of UC include:

- Anti-inflammatory drugs
- Immunosuppressants
- Biologic agents including anti-TNFα agents and integrin receptor antagonists
- Janus kinase inhibitors

Additionally, antibiotics, antidiarrheals, pain relievers, and iron supplements may be used in the treatment of UC (Mayo Clinic 2021b).

If diet, lifestyle changes, or drug therapy do not relieve signs and symptoms of UC, surgery may be recommended. Surgery can often eliminate UC but involves complete removal of potential disease-bearing tissue and may require removing the entire colon and rectum (Mayo Clinic 2021b).

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

The natural course of UC is characterized by periods of flare alternating with periods of remission. The severity of flares and their response to treatment vary among patients, can be hard to predict, and range from minor symptoms to life-threatening fulminant colitis that requires colectomy. During the course of the disease, extraintestinal manifestations are observed in up to 31% of patients (Cosnes 2011). The majority of patients have a mild-moderate disease course, which is most active at diagnosis, followed by varying periods of remission or mild activity; the cumulative risk of relapse is 70% to 80% at 10 years. Almost 50% of patients require UC-related hospitalization (Fumery 2018). In general, over a 10-year period, 50% to 55% of patients remit, approximately 37% follow a chronic, intermittent course, 6% develop a chronic continuous course, and only 1% have a period of low activity followed

by a severe increase (Fumery 2018). Approximately 20% to 30% of patients require a colectomy after 25 years of disease activity (Gajendran 2019).

Mortality

A Swedish study reported an incidence of 16.5 per 1,000 PY (95% CI 16.2 to 16.9) and an HR of 1.4 (95% CI 1.4 to 1.5) for all-cause mortality in UC for the years 1964 to 2014 (Olén 2020). A prospective IBD register in the catchment area of Finland which followed a set of UC patients from 1986 to 2007 reported an SMR of 0.90 (95% CI 0.77 to 1.06) (Manninen 2012). A Spanish study reported a mortality rate of 19.4 per 100,000 population in 2016 (Brunet 2018). For cause-specific mortality, the risk of death in diseases of the digestive system was nonsignificantly increased for UC (SMR=2.1). The SMR for colorectal cancer in UC was 1.8 and was 2.1 for disorders of the digestive system.

Important Co-morbidities:

Co-morbidities that occur in UC patients include small bowel or colorectal cancer; uveitis; episcleritis; arthritis; hepatobiliary disorders; infections such as *Helicobacter pylori* and cytomegalovirus; celiac disease; pancreatic disease; obesity; CV conditions including VTE and atherosclerosis; and anxiety and mood disorders (Román 2011; Burisch 2013).

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 (Kuenzig 2022). Trends in incidence are likely multifactorial and include changing environmental exposures, access to specialist care, and improved imaging (Khan 2023). 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 (Kuenzig 2022). 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 (Kuenzig 2022).

The most marked increases in the incidence of CD in Europe have been among adolescent age groups rather than among infants and younger children (Roberts 2020), with similar findings in the US (Ye 2020). In Canada, the incidence of very early onset CD is increasing faster than the incidence of CD in other age groups (Khan 2023).

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 (Kuenzig 2022), and 45.9 in the US (Ye 2020). Using US insurance claims data, Lewis (2023) 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 (Khan 2023).

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 (Greuter 2020). In a study of children with IBD diagnosed before their seventeenth birthday from all pediatric gastroenterology centers in Scotland, Van Limbergen (2008) 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) 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 (Sauer 2009).

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 (Agrawal 2021).

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 (Turner 2021; van Rheenen 2021). 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 (Bouhuys 2023).

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 (Duricova 2017). 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 (Day 2012b). 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 (Ley 2022).

Mortality

Studies conducted in Danish (Jess 2013) and Swedish (Olén 2019) 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 (Olén 2019).

Important Co-morbidities:

Pediatric patients with CD often experience growth impairment and may experience pubertal delay (Bouhuys 2023). Other common comorbidities include arthritis, thyroid disease, atopic dermatitis, autoimmune hepatitis, nephrolithiasis, and pancreatitis (Ghersin 2020; Vadstrup 2020).

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

The nonclinical safety studies performed showed that ustekinumab was well tolerated in general toxicity, developmental toxicity, and reproductive toxicity studies following weekly IV or twice-weekly SC dosing at doses up to 45 mg/kg. These studies did not identify toxicity in target organs or safety concerns requiring additional studies. The sections below discuss nonclinical safety studies for which there is limited clinical information or potentially a theoretical risk of clinical relevance, despite, in some cases, the negative results of the studies.

The nonclinical safety program for ustekinumab, a mAb to the shared p40 subunit of IL-12 and IL-23, was designed in accordance with the International Council for Harmonisation (ICH) S6 guidelines (1998).

Key Safety Findings	Relevance to Human Usage
Toxicity	
Repeat-dose toxicity	
Nonclinical safety studies showed that ustekinumab was well tolerated in general, developmental, and reproductive toxicity studies following weekly IV or twice weekly SC dosing at doses up to 45 mg/kg. Repeat-dose toxicity studies (1-month IV and 6-month SC) were conducted in predominately juvenile animals based on age at study initiation.	Animal studies suggest a large safety margin for humans administered ustekinumab intravenously and subcutaneously (up to 7.5- and 45-fold higher than the human dose, respectively).
Reproductive toxicity	
Repeated dose toxicology studies conducted in cynomolgus monkeys showed no toxicological effects of ustekinumab on reproductive organs. The no-observed-adverse-effect level (NOAEL) of ustekinumab for general toxicity and reproductive function of male cynomolgus monkeys was 45 mg/kg, approximately 45-fold higher than the anticipated human dose. In a female fertility study conducted in mice using an anti-mouse IL-12/23p40 mAb no adverse effects on female fertility were identified.	Results of reproductive toxicity studies suggest that administration of ustekinumab is unlikely to adversely affect male or female fertility.
Developmental toxicity	
The NOAEL of ustekinumab for maternal toxicity and for development of the conceptus was 45 mg/kg following weekly IV dosing or twice weekly SC dosing of pregnant monkeys, approximately 45-fold higher than the anticipated human dose.	Results of developmental toxicity studies suggest that administration of ustekinumab will not adversely affect mothers or their offspring.

Key Safety Findings	Relevance to Human Usage
Genotoxicity Genotoxicity studies have not been conducted with ustekinumab. The standard battery of assays recommended for small molecules is primarily designed to detect substances that interact with deoxyribonucleic acid (DNA) and induce gene mutations, chromosome aberrations and/or DNA damage and is not applicable to biotechnology-derived pharmaceuticals (ICH S6).	Monoclonal antibodies such as ustekinumab are not expected to pass through the cellular and nuclear membranes of intact cells and interact with DNA or other chromosomal material; therefore, potential genotoxicity is unlikely.
Carcinogenicity The risk of malignancy is a safety concern for immune modulating drugs in general. Carcinogenicity studies were not conducted with ustekinumab. Direct evaluation of carcinogenic potential of ustekinumab in carcinogenicity studies is precluded by its limited species reactivity. Ustekinumab only binds human and non-human primate IL-12p40 but does not bind to or neutralize IL-12 or IL-23 from mice or rats. There are no validated non-rodent models of carcinogenicity. Studies suggesting malignancy risk from antagonism of IL-12 include experiments using primarily mouse nonclinical tumor models. These studies have typically shown anti-tumor activity of exogenously administered IL-12 (Brunda 1993) or demonstrated compromised host defense to neoplasia following either antagonism of rodent IL-12 activity by anti-murine IL-12 antibodies or genetic ablation of IL-12 activity in knockout mice (Airoldi 2005). While data from these studies suggest a possible carcinogenic hazard associated with IL-12 antagonism, they are not adequate or validated to support a carcinogenic risk assessment.	There is a theoretical risk of malignancy associated with administration of ustekinumab based on the scientific literature pertaining to antagonism of IL-12/23p40. Malignancy is an important potential risk for ustekinumab.
<u>Other</u> **Hepatotoxicity and nephrotoxicity** No evidence of hepatotoxicity or nephrotoxicity was observed in toxicity studies based on clinical pathology and histopathology evaluations.	Results from 1-month IV and 6-month SC general toxicity studies suggest that administration of ustekinumab is unlikely to cause hepatotoxicity and nephrotoxicity. Animal studies suggest that there is a large safety margin for humans administered ustekinumab intravenously and subcutaneously (up to 7.5- and 45-fold higher than the human dose, respectively).

Key Safety Findings	Relevance to Human Usage
Infection The risk of infection is a safety concern for immune modulating drugs in general. Host-resistance studies were not conducted with ustekinumab because there are no validated non-rodent models of infection in which ustekinumab would have pharmacological activity. Published rodent studies suggesting infection risk from inhibition of Th1 or Th17 indicated that IL-12 and IL-23 may contribute to protective immune responses to viral, bacterial, intracellular protozoa, and fungal pathogens (Bowman 2006; Torti 2007). One of the 16 monkeys in the high-dose (45 mg/kg group) developed bacterial enteritis in Week 26 of the 6-month SC toxicology study. The possibility of ustekinumab-related contribution to this infection could not be excluded.	There is a theoretical risk of infection associated with administration of ustekinumab based on the scientific literature pertaining to inhibition of IL-12/23p40. Serious infections (including mycobacterial and salmonella infections) is an important potential risk for ustekinumab.

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

STELARA has been developed and marketed for the treatment of adult and pediatric (≥6 years of age) patients with moderate to severe plaque psoriasis, the treatment of adult patients with active PsA, the treatment of adult patients with moderate to severe CD, the treatment of adult patients with moderately to severely active UC, and the treatment of pediatric patients weighing at least 40 kg with moderately to severely active CD.

SIII.2. Clinical Trial Exposure

Tables SIII.1 through SIII.8 present available integrated exposure data across indications based on a data lock point of 11 February 2022 for the adult trials and 12 January 2024 for the pediatric trials.

Ustekinumab is dosed for psoriasis and PsA at 0, 4, and 16 weeks and every 12 weeks thereafter. It is assumed that drug exposure occurs up to the time of the next scheduled dose 12 weeks later. For example, subjects who received ustekinumab at Week 16 were estimated to be exposed until Week 28, when the next dose was scheduled. These calculations of exposure are appropriate based on the half-life of ustekinumab of approximately 3 weeks. The visit window of ±1 to 2 weeks was also taken into consideration.

The Phase 2 psoriasis trial C0379T04 included a 20-week placebo-controlled period; subjects were considered to have had 6 months of exposure in the controlled period if the duration between the first and last ustekinumab administrations was at least 14 weeks. The following convention was used to calculate exposure:

- Subjects in whom the duration between the first and last ustekinumab administrations was at least 14 weeks were counted as having 6 months of exposure, and subjects in whom the duration between the first and last ustekinumab administrations was at least 38 weeks were counted as having 1 year of exposure.
- Subjects with at least 62 weeks between the first and last ustekinumab administrations were counted as having at least 18 months of exposure.
- Subjects with at least 88 weeks between the first and last ustekinumab administrations were counted as having at least 2 years exposure.
- Subjects with at least 140 weeks between the first and last ustekinumab administrations were counted as having at least 3 years of exposure.
- Subjects with at least 192 weeks between the first and last ustekinumab administrations were counted as having at least 4 years exposure.
- Subjects with at least 240 weeks between the first and last ustekinumab administrations were considered to have at least 5 years exposure.

Exposure During Controlled Portions of Clinical Trials

Tables SIII.1 through SIII.4 present data from the controlled portions of the clinical trials completed at the data lock point.

The exposure data are presented for the following adult and pediatric trials:

- Psoriasis: C0379T02, C0379T04, C0743T08, C0743T09, C0743T12, C0743T23, C0743T25, and JNS009-JPN-02
  - Two trials were conducted in Japan: JNS009-JPN-01 and JNS009-JPN-02. Exposure data from JNS009-JPN-02 are included in the integrated tables. Exposure data from JNS009-JPN-01 are not presented, as this dataset was in Japanese and not available for pooling.
- Pediatric psoriasis: CNTO1275PSO3006
- PsA: C0743T10, CNTO1275PSA3001, and CNTO1275PSA3002
- CD: C0379T07, C0743T26, CNTO1275CRD3001, and CNTO1275CRD3002
- UC: CNTO1275UCO3001 induction

For Table SIII.3, note that the 6.0 mg/kg dose for CD (CNTO1275CRD3001 and CNTO1275CRD3002) and UC (CNTO1275UCO3001 induction) is a weight-range-based dose. Also note that in the pediatric psoriasis trial (CNTO1275PSO3006), 2 distinct weight-based ustekinumab dosages were studied, the standard dosage and the half-standard dosage, as outlined below.

Ustekinumab Dosages in CNTO1275PSO3006

Subject Body Weight	Standard Dosage	Half-standard Dosage
≤60 kg	0.75 mg/kg	0.375 mg/kg
>60 kg through ≤100 kg	45 mg	22.5 mg
>100 kg	90 mg	45 mg

Table SIII.1: Summary of Subject-years of Follow-up After Ustekinumab Exposure During Controlled Portions of Clinical Trials; Treated Subjects Across Indications: Adult and Pediatric Trials

	Subjects Treated	Total Subject-years of Follow-up
Psoriasis studies[a]		
Subjects treated with ustekinumab	2501	625
Duration of ustekinumab exposure		
≥ 6 months[b]	85	33
≥ 1 year[c]	0	0
Pediatric psoriasis study[a]		
Subjects treated with ustekinumab	73	17
Duration of ustekinumab exposure		
≥ 6 months[b]	0	0
≥ 1 year[c]	0	0
PsA studies[a]		
Subjects treated with ustekinumab	692	209
Duration of ustekinumab exposure		
≥ 6 months[b]	0	0
≥ 1 year[c]	0	0
Crohn's disease studies[a]		
Subjects treated with ustekinumab	1387	218
Duration of ustekinumab exposure		
≥ 6 months[b]	0	0
≥ 1 year[c]	0	0
Ulcerative colitis study[a]		
Subjects treated with ustekinumab	641	100
Duration of ustekinumab exposure		
≥ 6 months[b]	0	0
≥ 1 year[c]	0	0
All studies[a]		
Subjects treated with ustekinumab	5294	1169
Duration of ustekinumab exposure		
≥ 6 months[b]	85	33
≥ 1 year[c]	0	0

a: Psoriasis studies include C0379T02, C0379T04, C0743T08, C0743T09, C0743T12, C0743T23, C0743T25, and JNS009-JPN-02. PsA studies include C0743T10, CNTO1275PsA3001, and CNTO1275PsA3002. Crohn's disease studies include C0379T07, C0743T26, CNTO1275CRD3001 and CNTO1275CRD3002. Pediatric psoriasis study includes CNTO1275PSO3006. Ulcerative Colitis study includes CNTO1275UCO3001 (Induction Study).

b: The duration between the first and last ustekinumab administration was at least 14 weeks.

c: The duration between the first and last ustekinumab administration was at least 38 weeks.

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Table SIII.2: Summary of Subject-years of Follow-up After Ustekinumab Exposure During Controlled Portions of Clinical Trials by Age and Sex; Treated Subjects Across Indications: Adult and Pediatric Trials

	Male		Female	
	Subjects Treated	Total Subject-years of Follow-up	Subjects Treated	Total Subject-years of Follow-up
Psoriasis studies[a]				
Age (yrs)				
< 45	824	205	383	95
≥ 45 to < 65	817	204	339	85
≥ 65	88	23	50	13
Pediatric psoriasis study[a]				
Age (yrs)				
≥ 12 to ≤ 15	17	4	23	5
> 15 to < 18	17	4	16	4
PsA studies[a]				
Age (yrs)				
< 45	159	48	110	34
≥ 45 to < 65	184	56	188	57
≥ 65	20	6	31	9
Crohn's disease studies[a]				
Age (yrs)				
< 45	426	66	535	84
≥ 45 to < 65	140	22	235	37
≥ 65	22	3	29	5
Ulcerative colitis study[a]				
Age (yrs)				
< 45	207	32	155	24
≥ 45 to < 65	158	25	87	14
≥ 65	20	3	14	2
All studies[a]				
Age (yrs)				
≥ 12 to ≤ 15	17	4	23	5
> 15 to < 18	17	4	16	4
≥ 18 to < 45	1616	352	1183	238
≥ 45 to < 65	1299	306	849	192
≥ 65	150	35	124	28

a: Psoriasis studies include C0379T02, C0379T04, C0743T08, C0743T09, C0743T12, C0743T23, C0743T25, and JNS009-JPN-02. PsA studies include C0743T10, CNTO1275PsA3001, and CNTO1275PsA3002. Crohn's disease studies include C0379T07, C0743T26, CNTO1275CRD3001 and CNTO1275CRD3002. Pediatric psoriasis study includes CNTO1275PSO3006. Ulcerative Colitis study includes CNTO1275UCO3001 (Induction Study).

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Table SIII.3: Summary of Subject-years of Follow-up After Ustekinumab Exposure During Controlled Portions of Clinical Trials by Dose Level; Treated Subjects Across Indications: Adult and Pediatric Trials

	Subjects Treated	Total Subject-years of Follow-up
Psoriasis studies[a]		
0.27 mg/kg	5	2
0.675 mg/kg	4	2
1.35 mg/kg	4	2
2.7 mg/kg	4	2
45 mg	1284	318
90 mg	1200	299
Pediatric psoriasis study[a]		
Standard dosage	36	9
Half-standard dosage	37	9
PsA studies[a]		
45 mg	308	96
63 mg	59	14
90 mg	325	100
Crohn's disease studies[a]		
1.0 mg/kg	130	21
3.0 mg/kg	133	21
4.5 mg/kg	27	4
6.0 mg/kg	601	94
90 mg	25	4
130 mg	471	74
Ulcerative colitis study[a]		
6.0 mg/kg	320	50
130 mg	321	50
All studies[a]		
Standard dosage	36	9
Half-standard dosage	37	9
0.27 mg/kg	5	2
0.675 mg/kg	4	2
1.0 mg/kg	130	21
1.35 mg/kg	4	2
2.7 mg/kg	4	2
3.0 mg/kg	133	21
4.5 mg/kg	27	4
6.0 mg/kg	921	144
45 mg	1592	414
63 mg	59	14
90 mg	1550	403
130 mg	792	125

a: Psoriasis studies include C0379T02, C0379T04, C0743T08, C0743T09, C0743T12, C0743T23, C0743T25, and JNS009-JPN-02. PsA studies include C0743T10, CNTO1275PsA3001, and CNTO1275PsA3002. Crohn's disease studies include C0379T07, C0743T26, CNTO1275CRD3001 and CNTO1275CRD3002. Pediatric psoriasis study includes CNTO1275PSO3006. Ulcerative Colitis study includes CNTO1275UCO3001 (Induction Study).

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Table SIII.4: Summary of Subject-years of Follow-up After Ustekinumab Exposure During Controlled Portions of Clinical Trials by Race; Treated Subjects Across Indications: Adult and Pediatric Trials

	Subjects Treated	Total Subject-years of Follow-up
Psoriasis studies[ab]		
Race		
White	1981	501
Black or African American	49	12
Asian	285	67
American Indian or Alaskan native	0	0
Native Hawaiian or other Pacific Islander	0	0
Other	60	15
Unknown	0	0
Not reported	0	0
Pediatric psoriasis study[a]		
Race		
White	64	15
Black or African American	0	0
Asian	4	1
American Indian or Alaskan native	2	0
Native Hawaiian or other Pacific Islander	0	0
Other	2	0
Unknown	1	0
Not reported	0	0
PsA studies[a]		
Race		
White	668	202
Black or African American	4	1
Asian	11	3
American Indian or Alaskan native	0	0
Native Hawaiian or other Pacific Islander	0	0
Other	8	2
Unknown	0	0
Not reported	0	0
Crohn's disease studies[a]		
Race		
White	1203	189
Black or African American	45	7
Asian	83	13
American Indian or Alaskan native	1	0
Native Hawaiian or other Pacific Islander	2	0
Other	35	5
Unknown	2	0
Not reported	16	3
Ulcerative colitis study[a]		
Race		
White	481	75
Black or African American	6	1
Asian	96	15
American Indian or Alaskan native	0	0
Native Hawaiian or other Pacific Islander	0	0
Other	21	3
Unknown	3	0
Not reported	34	5

Table SIII.4: Summary of Subject-years of Follow-up After Ustekinumab Exposure During Controlled Portions of Clinical Trials by Race; Treated Subjects Across Indications: Adult and Pediatric Trials

	Subjects Treated	Total Subject-years of Follow-up
All studies[ab]		
Race		
White	4397	982
Black or African American	104	21
Asian	479	100
American Indian or Alaskan native	3	1
Native Hawaiian or other Pacific Islander	2	0
Other	126	26
Unknown	6	1
Not reported	50	8

a: Psoriasis studies include C0379T02, C0379T04, C0743T08, C0743T09, C0743T12, C0743T23, and C0743T25. PsA studies include C0743T10, CNTO1275PsA3001, and CNTO1275PsA3002. Crohn's disease studies include C0379T07, C0743T26, CNTO1275CRD3001 and CNTO1275CRD3002. Pediatric psoriasis study includes CNTO1275PSO3006. Ulcerative Colitis study includes CNTO1275UCO3001 (Induction Study).

b: JNS009-JPN-02 psoriasis study data is excluded from the summary because the race data was not collected for that study.

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Exposure in the All Clinical Trials Population

Tables SIII.5 through SIII.8 present data from all portions of the clinical trials completed at the data lock point.

The exposure data are presented for the following adult and pediatric trials:

- Psoriasis: C0379T01, C0379T02, C0379T04, C0743T08, C0743T09, C0743T12, C0743T23, C0743T25, and JNS009-JPN-02
  - The same caveat regarding trials that were conducted in Japan (JNS009-JPN-01 and JNS009-JPN-02) discussed above (see Exposure During Controlled Portions of Clinical Trials section) also applies here.
- Pediatric psoriasis: CNTO1275PSO3006 and CNTO1275PSO3013 (through Week 176)
- PsA: C0743T10, CNTO1275PSA3001, and CNTO1275PSA3002
- Adult CD: C0379T07, C0743T26, CNTO1275CRD3001, CNTO1275CRD3002, and CNTO1275CRD3003 (Week 272 database lock)
- UC: CNTO1275UCO3001 induction and CNTO1275UCO3001 maintenance (Week 220 database lock)
- Pediatric CD: CNTO1275CRD1001 and CNTO1275CRD3004 (Week 44 interim database lock)

The caveats regarding weight-range-based doses for CD, UC, and pediatric psoriasis trials (see Exposure During Controlled Portions of Clinical Trials section) (CD: CNTO1275CRD3001 and CNTO1275CRD3002; UC: CNTO1275UCO3001 [induction]; pediatric psoriasis: CNTO1275PSO3006) also apply for Table SIII.7. In the pediatric psoriasis trial CNTO1275PSO3006, 2 distinct weight-based ustekinumab doses were studied – a standard dose and a half-standard dose. In the pediatric psoriasis trial CNTO1275PSO3013, all subjects received the standard weight-based dose as used in CNTO1275PSO3006. In the pediatric CD trial CNTO1275CRD1001, 2 distinct weight-based ustekinumab doses were studied – a low dose and a high dose. In the pediatric CD trial CNTO1275CRD3004, subjects with body weight ≥40 kg received the standard weight-based dose.

Ustekinumab Doses in CNTO1275CRD1001		
Subject Body Weight	**Low Dose**	**High Dose**
<40 kg	3 mg/kg	9 mg/kg
≥40 kg	130 mg	390 mg

Ustekinumab Doses in CNTO1275CRD3004	
Subject Body Weight	**Standard Dose**
≥40 kg to ≤55 kg	260 mg
>55 kg to ≤85 kg	390 mg
>85 kg	520 mg

Table SIII.5: Summary of Subject-Years of Follow-Up After Ustekinumab Exposure in All Clinical Trials Population; Treated Subjects Across Indications: Adult and Pediatric Trials

	Subjects Treated	Total Subject-years of Follow-up
Psoriasis studies[a]		
Subjects treated with ustekinumab	3740	9455
Duration of ustekinumab exposure		
≥ 6 months[b]	2774	8947
≥ 1 year[c]	1993	8313
≥ 2 years[d]	1653	7858
≥ 3 years[e]	1569	7652
≥ 4 years[f]	1482	7341
≥ 5 years[g]	838	4259
Pediatric psoriasis studies[a]		
Subjects treated with ustekinumab	154	203
Duration of ustekinumab exposure		
≥ 6 months[b]	152	203
≥ 1 year[c]	106	165
≥ 2 years[d]	21	65
≥ 3 years[e]	13	43
PsA studies[a]		
Subjects treated with ustekinumab	1018	1403
Duration of ustekinumab exposure		
≥ 6 months[b]	843	1316
≥ 1 year[c]	701	1210
≥ 2 years[d]	289	603
Crohn's disease studies[a]		
Subjects treated with ustekinumab	1823	3124
Duration of ustekinumab exposure		
≥ 6 months[b]	691	2446
≥ 1 year[c]	592	2362
≥ 2 years[d]	496	2225
≥ 3 years[e]	421	2038
≥ 4 years[f]	363	1839
≥ 5 years[g]	310	1602
Pediatric Crohn's disease studies[a]		
Subjects treated with ustekinumab	82	126
Duration of ustekinumab exposure		
≥ 6 months[b]	77	124
≥ 1 year[c]	63	115
≥ 2 years[d]	18	64
≥ 3 years[e]	12	50
≥ 4 years[f]	9	40
≥ 5 years[g]	1	5
Ulcerative colitis study[a]		
Subjects treated with ustekinumab	826	2134
Duration of ustekinumab exposure		
≥ 6 months[b]	547	1885
≥ 1 year[c]	500	1849
≥ 2 years[d]	433	1752
≥ 3 years[e]	383	1627
≥ 4 years[f]	349	1509
All studies[a]		
Subjects treated with ustekinumab	7643	16446

Table SIII.5: Summary of Subject-Years of Follow-Up After Ustekinumab Exposure in All Clinical Trials Population; Treated Subjects Across Indications: Adult and Pediatric Trials

Duration of ustekinumab exposure	Subjects Treated	Total Subject-years of Follow-up
≥ 6 months[b]	5084	14921
≥ 1 year[c]	3955	14014
≥ 2 years[d]	2910	12566
≥ 3 years[e]	2398	11410
≥ 4 years[f]	2203	10729
≥ 5 years[g]	1149	5866

[a] Psoriasis studies include C0379T01, C0379T02, C0379T04, C0743T08, C0743T09, C0743T12, C0743T23, C0743T25, and JNS009-JPN-02. Pediatric psoriasis studies include CNTO1275PSO3006 and CNTO1275PSO3013. PsA studies include C0743T10, CNTO1275PsA3001, and CNTO1275PsA3002. Crohn's disease studies include C0379T07, C0743T26, CNTO1275CRD3001, CNTO1275CRD3002, and CNTO1275CRD3003 (Week 272 Database Lock). Pediatric Crohn's disease studies include CNTO1275CRD1001 (Week 268 DBL) and CNTO1275CRD3004 (48 subjects ≥ 40 kg through Week M-44). Ulcerative Colitis study includes CNTO1275UCO3001 (Induction Study and Maintenance Study through Week 220 Database Lock).
[b] The duration between the first and last ustekinumab administration was at least 14 weeks.
[c] The duration between the first and last ustekinumab administration was at least 38 weeks.
[d] The duration between the first and last ustekinumab administration was at least 88 weeks.
[e] The duration between the first and last ustekinumab administration was at least 140 weeks.
[f] The duration between the first and last ustekinumab administration was at least 192 weeks.
[g] The duration between the first and last ustekinumab administration was at least 240 weeks.

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Table SIII.6: Summary of Subject-Years of Follow-Up After Ustekinumab Exposure in All Clinical Trials Population by Age and Gender; Treated Subjects Across Indications: Adult and Pediatric Trials

	Male		Female	
	Subjects Treated	Total Subject-years of Follow-up	Subjects Treated	Total Subject-years of Follow-up
Psoriasis studies[a]				
Age (yrs)				
< 45	1273	3027	544	1294
≥ 45 to < 65	1217	3286	496	1355
≥ 65	138	311	72	182
Pediatric psoriasis studies[a]				
Age (yrs)				
≥ 6 to < 12	17	32	27	59
≥ 12 to ≤ 15	26	25	29	32
> 15 to < 18	28	29	27	26
PsA studies[a]				
Age (yrs)				
< 45	235	339	155	219
≥ 45 to < 65	275	372	284	389
≥ 65	26	28	43	57
Crohn's disease studies[a]				
Age (yrs)				
< 45	566	988	673	1101
≥ 45 to < 65	212	351	310	584
≥ 65	27	40	35	60
Pediatric Crohn's disease studies[a]				
Age (yrs)				
≥ 2 to < 6	0	-	0	-
≥ 6 to < 12	7	17	3	6
≥ 12 to < 18	33	41	39	62
Ulcerative colitis study[a]				
Age (yrs)				
< 45	275	737	202	491
≥ 45 to < 65	198	513	108	292
≥ 65	27	60	16	40
All studies[a]				
Age (yrs)				
≥ 2 to < 6	0	-	0	-
≥ 6 to < 12	24	49	30	65
≥ 12 to < 18	87	95	95	120
≥ 18 to < 45	2349	5091	1574	3105
≥ 45 to < 65	1902	4522	1198	2621
≥ 65	218	439	166	338

[a] Psoriasis studies include C0379T01, C0379T02, C0379T04, C0743T08, C0743T09, C0743T12, C0743T23, C0743T25, and JNS009-JPN-02. Pediatric psoriasis studies include CNTO1275PSO3006 and CNTO1275PSO3013. PsA studies include C0743T10, CNTO1275PsA3001, and CNTO1275PsA3002. Crohn's disease studies include C0379T07, C0743T26, CNTO1275CRD3001, CNTO1275CRD3002, and CNTO1275CRD3003 (Week 272 Database Lock). Pediatric Crohn's disease studies include CNTO1275CRD1001 (Week 268 DBL) and CNTO1275CRD3004 (48 subjects ≥ 40 kg through Week M-44). Ulcerative Colitis study includes CNTO1275UCO3001 (Induction Study and Maintenance Study through Week 220 Database Lock).

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Table SIII.7: Summary of Subject-Years of Follow-Up After Ustekinumab Exposure in All Clinical Trials Population by Dose Level; Treated Subjects Across Indications: Adult and Pediatric Trials

	Subjects Treated	Total Subject-years of Follow-up
Psoriasis studies[a]		
0.09 mg/kg	4	1
0.27 mg/kg	9	3
0.675 mg/kg	4	2
0.9 mg/kg	5	2
1.35 mg/kg	4	2
2.7 mg/kg	4	2
4.5 mg/kg	5	2
45 mg[b]	1832	4118
90 mg[b]	2076	5325
Pediatric psoriasis studies[a]		
Standard dosage	98	147
Half-standard dosage	56	56
PsA studies[a]		
45 mg[c]	577	773
63 mg	116	64
90 mg[c]	381	567
Crohn's disease studies[a]		
1.0 mg/kg[d]	130	51
3.0 mg/kg[d]	133	51
4.5 mg/kg	59	26
6.0 mg/kg[d]	601	209
90 mg[d]	1189	2530
130 mg[d]	754	217
270 mg[d]	85	40
Pediatric Crohn's disease studies[a,e]		
3.0 mg/kg	10	23
9.0 mg/kg	6	14
130 mg	8	22
260 mg	25	23
390 mg	33	44
Ulcerative colitis study[a]		
6.0 mg/kg[f]	504	328
90 mg[f]	581	1636
130 mg[f]	321	168
All studies[a]		
Standard dosage	98	147
Half-standard dosage	56	56
0.09 mg/kg	4	1
0.27 mg/kg	9	3
0.675 mg/kg	4	2
0.9 mg/kg	5	2
1.0 mg/kg[d]	130	51
1.35 mg/kg	4	2
2.7 mg/kg	4	2
3.0 mg/kg[d,e]	143	74
4.5 mg/kg	64	28
6.0 mg/kg[d,f]	1105	537
9.0 mg/kg[e]	6	14
45 mg[b,c]	2409	4891
63 mg	116	64

Table SIII.7: Summary of Subject-Years of Follow-Up After Ustekinumab Exposure in All Clinical Trials Population by Dose Level; Treated Subjects Across Indications: Adult and Pediatric Trials

	Subjects Treated	Total Subject-years of Follow-up
90 mg[b,c,d,f]	4227	10057
130 mg[f]	1083	408
260 mg[e]	25	23
270 mg[d]	85	40
390 mg[e]	33	44

[a] Psoriasis studies include C0379T01, C0379T02, C0379T04, C0743T08, C0743T09, C0743T12, C0743T23, C0743T25, and JNS009-JPN-02. Pediatric psoriasis studies include CNTO1275PSO3006 and CNTO1275PSO3013. PsA studies include C0743T10, CNTO1275PsA3001, and CNTO1275PsA3002. Crohn's disease studies include C0379T07, C0743T26, CNTO1275CRD3001, CNTO1275CRD3002, and CNTO1275CRD3003 (Week 272 Database Lock). Pediatric Crohn's disease studies include CNTO1275CRD1001 (Week 268 DBL) and CNTO1275CRD3004 (48 subjects ≥ 40 kg through Week M-44). Ulcerative Colitis study includes CNTO1275UCO3001 (Induction Study and Maintenance Study through Week 220 Database Lock).
[b] For C0743T09, subjects who were dose escalated from 45 mg to 90 mg were switched to the corresponding row following dose escalation.
[c] For CNTO1275PsA3001 and CNTO1275PsA3002, subjects who were dose escalated from 45 mg to 90 mg were switched to the corresponding row following dose escalation.
[d] For C0743T26, subjects assigned to the 1 mg/kg, 3 mg/kg, and 6 mg/kg induction groups were switched to the 90 mg row following a dose change to 90 mg. Placebo subjects who crossed over to 270 mg were not switched to the 90 mg row following a dose change to 90 mg.
[e] For CNTO1275CRD1001 and CNTO1275CRD3004, subjects who entered the maintenance phase after induction phase, were counted at both dosing periods.
[f] For CNTO1275CRD3003 and CNTO1275UCO3001, subjects who entered the maintenance phase after induction phase, were counted at both dosing periods.

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Table SIII.8 Summary of Subject-Years of Follow-Up After Ustekinumab Exposure in All Clinical Trials Population by Race; Treated Subjects Across Indications: Adult and Pediatric Trials

	Subjects Treated	Total Subject-years of Follow-up
Psoriasis studies[a,b]		
Race		
White	2906	8336
Black or African American	64	185
Asian	530	535
American Indian or Alaskan native	0	0
Native Hawaiian or other Pacific Islander	0	0
Other	86	201
Unknown	0	0
Not reported	0	0
Pediatric psoriasis studies[a]		
Race		
White	138	183
Black or African American	0	0
Asian	7	8
American Indian or Alaskan native	3	3
Native Hawaiian or other Pacific Islander	0	0
Other	4	4
Unknown	1	0
Not reported	1	4

Table SIII.8 Summary of Subject-Years of Follow-Up After Ustekinumab Exposure in All Clinical Trials Population by Race; Treated Subjects Across Indications: Adult and Pediatric Trials

	Subjects Treated	Total Subject-years of Follow-up
PsA studies[a]		
Race		
White	985	1358
Black or African American	5	6
Asian	15	23
American Indian or Alaskan native	0	0
Native Hawaiian or other Pacific Islander	0	0
Other	12	14
Unknown	0	0
Not reported	0	0
Crohn's disease studies[a]		
Race		
White	1584	2682
Black or African American	63	82
Asian	108	259
American Indian or Alaskan native	1	1
Native Hawaiian or other Pacific Islander	2	3
Other	44	59
Unknown	4	7
Not reported	17	30
Pediatric Crohn's disease studies[a]		
Race		
White	73	111
Black or African American	1	0
Asian	3	2
American Indian or Alaskan native	0	0
Native Hawaiian or other Pacific Islander	0	0
Other	2	9
Unknown	1	1
Not reported	2	2
Ulcerative colitis study[a]		
Race		
White	623	1630
Black or African American	8	14
Asian	127	331
American Indian or Alaskan native	0	0
Native Hawaiian or other Pacific Islander	0	0
Other	27	71
Unknown	3	2
Not reported	38	85
All studies[a,b]		
Race		
White	6309	14301
Black or African American	141	288
Asian	790	1159
American Indian or Alaskan native	4	4

Table SIII.8 Summary of Subject-Years of Follow-Up After Ustekinumab Exposure in All Clinical Trials Population by Race; Treated Subjects Across Indications: Adult and Pediatric Trials

	Subjects Treated	Total Subject-years of Follow-up
Native Hawaiian or other Pacific Islander	2	3
Other	175	359
Unknown	9	11
Not reported	58	121

[a] Psoriasis studies include C0379T01, C0379T02, C0379T04, C0743T08, C0743T09, C0743T12, C0743T23, C0743T25, and JNS009-JPN-02. Pediatric psoriasis studies include CNTO1275PSO3006 and CNTO1275PSO3013. PsA studies include C0743T10, CNTO1275PsA3001, and CNTO1275PsA3002. Crohn's disease studies include C0379T07, C0743T26, CNTO1275CRD3001, CNTO1275CRD3002, and CNTO1275CRD3003 (Week 272 Database Lock). Pediatric Crohn's disease studies include CNTO1275CRD1001 (Week 268 DBL) and CNTO1275CRD3004 (48 subjects ≥ 40 kg through Week M-44). Ulcerative Colitis study includes CNTO1275UCO3001 (Induction Study and Maintenance Study through Week 220 Database Lock).

[b] JNS009-JPN-02 psoriasis study data is excluded from the summary because the race data was not collected for that study.

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PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

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

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Criterion 1	**Had shown a previous immediate hypersensitivity response, including anaphylaxis, to an immunoglobulin product (eg, plasma derived or recombinant monoclonal antibody).**
Reason for being an exclusion criterion	Patients with a history of immediate hypersensitivity to an immunoglobulin product were excluded from ustekinumab trials to avoid potentially life-threatening hypersensitivity reactions.
Included as missing information?	No
Rationale (if not included as missing information)	It is not possible to predict which patients may develop a hypersensitivity reaction to STELARA. STELARA is contraindicated in patients with a known hypersensitivity to the active substance or to any of the excipients (SmPC section 4.3 [Contraindications]). Additional information regarding hypersensitivity reactions that may occur during treatment with STELARA is provided in SmPC section 4.4 (Special Warnings and Precautions for Use).
Criterion 2	**Clinically active infections including granulomatous infection (ie, tuberculosis [TB]), histoplasmosis or coccidioidomycosis), prior to screening.**
Criterion 3	**Had a history of chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection (eg, bronchiectasis), recurrent urinary tract infection (recurrent pyelonephritis or chronic nonremitting cystitis), or open, draining, or infected skin wounds or ulcers.**

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Criterion 4	**Herpes zoster infection within a specified time of trial medication.**
Reason for being an exclusion criterion	Treatment with immunomodulatory agents may increase the risk of infection or worsen an existing infection. The exclusion criterion related to herpes zoster was based on the potential safety concern of reactivation or dissemination of zoster with treatment with a selective immunosuppressant.
Included as missing information?	No
Rationale (if not included as missing information)	Serious infections (including mycobacterial and salmonella infections) is an important potential risk for STELARA. STELARA is contraindicated in patients with clinically important, active infection such as active TB (SmPC section 4.3 [Contraindications]). Clinical experience suggests the immunosuppression seen with ustekinumab is minimal; however, caution should be exercised when considering the use of ustekinumab in patients with a chronic infection or a history of recurrent infection. STELARA may have the potential to increase the risk of infections and reactivate latent infections (SmPC section 4.4 [Special Warnings and Precautions for Use]). Guidance for the management of subjects who develop infections while being treated with STELARA is provided in SmPC section 4.4 (Special Warnings and Precautions for Use). While herpes zoster has been recognized as an adverse drug reaction (ADR) for ustekinumab, there has been no evidence of clinically severe presentations, frequent dissemination, or increased reactivations in clinical experience.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Criterion 5	**Were pregnant, nursing, or planning pregnancy during the trial and for a specified time thereafter.**
Reason for being an exclusion criterion	Per ICH guidance, pregnant women are generally excluded from clinical trials. It was unknown whether ustekinumab is excreted in human milk.
Included as missing information?	No
Rationale (if not included as missing information)	Exposure during pregnancy Guidance for the use of STELARA during pregnancy is provided in SmPC section 4.6 (Fertility, Pregnancy and Lactation). Neither routine nor additional pharmacovigilance activities have identified any safety signals associated with the use of STELARA during pregnancy. The MAH considers that sufficient exposure data have been collected and does not consider exposure during pregnancy as missing information. Use during breastfeeding Guidance for the use of STELARA during breastfeeding is provided in SmPC section 4.6 (Fertility, Pregnancy and Lactation).
Criterion 6	**Had a transplanted organ (with exception of a corneal transplant >3 months prior to first administration of trial medication).**
Reason for being an exclusion criterion	This is typical, prudent, precautionary position when a drug has not been widely used in humans. Most patients who have undergone organ transplant require immunosuppressant medications that preclude inclusion in clinical trials.
Included as missing information?	No
Rationale (if not included as missing information)	Transplant patients generally receive immunosuppressive therapy to prevent rejection of the transplanted organ. Exposure to ustekinumab might increase the risk of complications from concomitant immunosuppression. Caution should be exercised when considering concomitant use of other immunosuppressants or when transitioning from other immunosuppressive biologics (SmPC section 4.4 [Special Warnings and Precautions for Use]).

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Criterion 7	**Had any known malignancy or have had a history of malignancy within the previous 5 years (except adequately treated cutaneous basal cell carcinoma or squamous cell carcinoma with no evidence of recurrence; cervical carcinoma in situ that has been treated with no evidence of recurrence, within 5 years prior to the first administration of trial medication).**
Criterion 8	**Had a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location.**
Reason for being an exclusion criterion	Treatment with an immunomodulatory agent may theoretically increase the risk of developing a malignancy. However, even with potent immunosuppressive agents, a causal relationship between immunosuppression and malignancy has not been established. A theoretical risk was recognized based on nonclinical data demonstrating anti IL-12 activity in mice. Therefore, patients with malignancy were excluded from ustekinumab clinical trials. Other immunosuppressive biologics have been associated with lymphoma. Therefore, patients with lymphoma were excluded from ustekinumab clinical trials.
Included as missing information?	No
Rationale (if not included as missing information)	All additional pharmacovigilance activities to investigate the use of ustekinumab in patients with concurrent malignancy or a history of malignancy have been completed. However, as immunosuppressants like ustekinumab have the potential to increase the risk of malignancy, guidance for the use of STELARA in patients with a history of malignancy and in patients who continue treatment after developing malignancy while receiving STELARA is provided in SmPC section 4.4 (Special Warnings and Precautions for Use).
Criterion 9	**Received a live virus or bacterial vaccination (including Bacillus of Calmette and Guérin [BCG]) within 3 to 12 months of screening, during the trial, and for up to 12 months after the last trial medication injection.**
Reason for being an exclusion criterion	Administration of live vaccines during immunomodulatory therapy may increase the risk of active infection following vaccination.
Included as missing information?	No

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Rationale (if not included as missing information)	Although clinical experience suggests that immunosuppression with ustekinumab is minimal, it is recommended that live viral or live bacterial vaccines not be given concurrently with STELARA (SmPC section 4.4 [Special Warnings and Precautions]).
Criterion 10	**Received allergy immunotherapy for prevention of anaphylactic reactions.**
Reason for being an exclusion criterion	At the time the Phase 3 clinical trial protocols were written, there was concern about a theoretical risk of decreased efficacy of allergy immunotherapy associated with IL-12/IL-23 blockade.
Included as missing information?	No
Rationale (if not included as missing information)	Routine pharmacovigilance has not identified any safety issues specific to this population. The safety of STELARA in patients who have undergone allergy immunotherapy is not currently being addressed through any additional pharmacovigilance activities, and there is no reasonable expectation that any pharmacovigilance activity can provide further characterization of the safety profile in this population.
Criterion 11	**Had current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease.**
Reason for being an exclusion criterion	This is typical, prudent, precautionary position, applied to clinical trial subjects when a drug has not been widely used in humans.
Included as missing information?	No
Rationale (if not included as missing information)	The impracticality of identifying adequate numbers of patients with progressive concomitant disease in each of these categories precludes the further study of STELARA in these patient populations. Given the severity of disease in subjects with severe, progressive, or uncontrolled hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, psychiatric, or cerebral disease, the risk-benefit balance of the use of STELARA should be carefully evaluated on a case-by-case basis.

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

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 Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women Breastfeeding women	Although prohibited by protocol, exposure to STELARA during pregnancy occurred in the clinical development program. Through 31 December 2023, 161 pregnancies through maternal exposure and 88 pregnancies through paternal exposure were reported from clinical trials. Breastfeeding women were not included in the clinical development program.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with CV 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	STELARA clinical trials have been conducted globally in a variety of ethnic groups. The majority of subjects in the STELARA clinical trials were white.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Pediatric patients	Exposure in pediatric psoriasis clinical trials: 71 males, 83 females. Exposure in pediatric CD clinical trials (patients weighing 40 kg and above): 40 males, 42 females.

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

SV.1.1. Method used to Calculate Exposure

Worldwide patient exposure (person-times estimates):

Patient exposure estimates were calculated from company distribution data and the amount of medication equivalent to 1 PY of exposure. The recommended dose of STELARA varies by country and region. Exposure in PY was calculated using posology in approved prescribing information, regional estimates based on usage of the low-versus-high dose, and patient compliance with dosing regimens.

Additional stratifications for ustekinumab exposure:

Stratification information for STELARA is limited. Information is provided using IQVIA (MIDAS™) data when possible and appropriate. Market research sources for nonstudy exposure data are unavailable for breakdowns such as use in pregnant or breastfeeding women, patients with hepatic impairment, and patients with renal impairment.

EU exposure by age and sex presented as a percentage of prescription sales:

Prescription sales stratified by age and sex available from IQVIA for the European Union (EU) are presented as a percentage of total prescription sales.

Exposure by indication presented as a percentage of prescription sales

Market research data are not available at this time to appropriately assess prescription sales stratified by indication for STELARA.

SV.1.2. Exposure

Table SV.1: Worldwide Cumulative Postauthorization Exposure to Ustekinumab (Launch through 31 December 2023)

Region	Total mg	Person-Years
European Union	351,366,102	1,499,408
United States	440,136,802	1,817,985
Canada	99,371,929	440,526
Rest of World	214,066,306	906,988
Total[a]	**1,104,941,139**	**4,664,907**

[a]: Includes 45 mg, 90 mg and 130 mg units. Person-years have been calculated using average yearly dose which can vary from one period to the next.

Table SV.2: Cumulative Postauthorization Exposure to Ustekinumab by Age Group as a Percentage of Prescription Sales in the European Union (01 July 2020 through 30 September 2023)

Age Groups (Years)[a]	European Union[b] (236,810 Prescriptions[c])
0 to 15	0.4%
16 to 35	26.0%
36 to 65	60.3%
≥66	13.3%

a: Regional prescription data by age are only available for the last 3 years ending September 2023).
b: Data stratified by age are only available for France, Germany, and Italy.
c: Includes retail channels.

Table SV.3: Cumulative Postauthorization Exposure to Ustekinumab by Age Group as a Percentage of Prescription Sales Outside the European Union (01 July 2020 through 30 September 2023)

Age Groups (Years)[a]	Non-European Union[b,c](1,549,115 Prescriptions[d])
0 to 15	3.1%
16 to 35	47.2%
36 to 65	41.5%
≥66	8.2%

a: Regional prescription data by age are only available for the last 3 years ending September 2023).
b: Data stratified by age are only available for Japan, United Kingdom, and the United States.
c: The United Kingdom is no longer a part of the European Union and has been grouped under rest of world from January 2021 onwards.
d: Includes retail channels.

Table SV.4: Cumulative Postauthorization Exposure to Ustekinumab by Sex as a Percentage of Prescription Sales (01 July 2020 through 30 September 2023)

Country	Females	Males	Patient Sex Unidentified
France (37,725 prescriptions[a])	41.9%	58.1%	0.0%
Germany (170,992 prescriptions[a])	51.0%	49.0%	0.0%
Italy (28,093 prescriptions[a])	49.3%	50.7%	0.0%
Japan (525,167 prescriptions[a])	42.0%	58.0%	0.0%
United Kingdom (42 prescriptions[a])	0.0%	0.0%	100.0%
United States (58,333 prescriptions[a])	55.1%	44.9%	0.0%

a: Includes retail channels.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

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 and pharmacodynamic properties of ustekinumab are not characteristic of drugs with high dependence potential (eg, 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.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

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

Not applicable.

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

Not applicable.

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

Not applicable.

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

Missing Information	Reason for Addition to the List of Safety Concerns
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. An LTE study of ustekinumab in pediatric clinical study participants (2 to <18 years of age; CNTO1275ISD3001 [UNITED] LTE) to collect long-term safety data in pediatric patients who receive SC ustekinumab for at least 1 year after participating in a primary pediatric ustekinumab trial (CNTO1275CRD1001, CNTO1275PUC3001, CNTO1275CRD3004, and CNTO1275JPA3001) is ongoing.

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

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 adult patients with moderately to severely active ulcerative colitis
- Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease

The methodology for identifying clinical events for the important identified and important potential risks is based on Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 and its subsequent versions.

The tables in Section SVII.3.1 present the proportion of subjects with relevant events by indication and include available ustekinumab Phase 1, Phase 2, and Phase 3 clinical trial data for the controlled periods, as well as through the end of the reporting periods. The percentage of subjects with 1 or more events associated with the specified risk is provided for the ustekinumab versus placebo/comparator group in each table. The number of subjects evaluated in the placebo/comparator group was the same in the Controlled Portions Populations and the All Clinical Trials Populations. The number of subjects evaluated in the ustekinumab group is greater in the All Clinical Trials Population column considering that in most of the trials, the placebo/comparator subjects crossed over to receive ustekinumab. A subject who was initially randomized to the placebo group and crossed over to ustekinumab treatment would be counted twice if the subject experienced the same event (ie, preferred term [PT]) in both phases of the trial. These subjects were not included in the Controlled Portions Population but were included the All Clinical Trials Population after they crossed over. The ORs and 95% CIs are provided to assess the impact of ustekinumab for the important identified and potential risks during the controlled portions of the clinical trials. The OR was not calculated if there were no events in either the ustekinumab or placebo/comparator treatment groups or if the total number of events in the ustekinumab and placebo/comparator groups was ≤5.

The proportion of subjects who experienced an event associated with an important identified or potential risk was also summarized by trial medication received through the end of the reporting periods. Caution is advised when interpreting data for these portions of the clinical trials as the average follow-up was generally longer for the ustekinumab-treated subjects than the subjects who received control agents. Additionally, the seriousness/outcomes and severity are summarized for ustekinumab-treated subjects.

For pediatric trials, data are shown only for risks in which events were reported ('Serious infections').

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

Important Identified Risks: None

Important Potential Risk: Serious Infections (Including Mycobacterial and Salmonella Infections)

Potential Mechanisms:

Studies performed in mice suggest that IL-12 may contribute to protective immune responses to intracellular protozoa, bacteria, and fungal pathogens (Trinchieri 2003), and IL-23 may contribute to immunity to *Klebsiella pneumonia* (Happel 2005), *Mycobacterium tuberculosis* (Khader 2005), *Cryptococcus neoformans* (Kleinschek 2006), and *Candida albicans* (Acosta-Rodriguez 2007). See also the discussion regarding infection in Module SII.

Humans who are genetically deficient for IL-12/23p40 or IL-12Rβ1 and who are presumed to be deficient in both IL-12 and IL-23 function have normal resistance to ubiquitous viruses and fungi, gram-positive and gram-negative bacteria, and common opportunistic protozoa. These individuals are susceptible to non-TB primary mycobacteria infection, including BCG, and recurring *Salmonella sp*. (Fieschi 2003; Novelli 2004). Filipe-Santos (2006) reviewed inborn errors of IL-12/23 and reported that these patients, when vaccinated with BCG, developed BCG disease. They also found that these patients were more susceptible to salmonella infections.

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. ‘Serious infections (including mycobacterial and salmonella infections)’ is considered an important potential risk with STELARA based upon the theoretical risk identified from nonclinical data and in humans who are genetically deficient for the cytokines that are inhibited by STELARA (IL-12/23p40 or IL-12Rβ1). However, the risk of developing serious infections (including mycobacterial and salmonella infections) in subjects on anti-IL-12/23p40 therapy such as STELARA is currently unknown.

Across clinical trials in all indications for which STELARA is approved, analysis of pooled data from the controlled periods does not suggest an increased risk of serious infection in the ustekinumab-treated population.

Characterization of the Risk – Data:

Table SVII.1: Important Potential Risk - Serious Infections; Treated Subjects Across Indications

	Psoriasis Studies[a]		PsA Studies[a]		Crohn's Disease Studies[a]		Ulcerative Colitis Study[a]		All Studies[a]	
	Controlled Portions Population (N=2375)	All Clinical Trials Population (N=3586)	Controlled Portions Population (N=692)	All Clinical Trials Population (N=1018)	Controlled Portions Population (N=1387)	All Clinical Trials Population (N=1823)	Controlled Portions Population (N=641)	All Clinical Trials Population (N=826)	Controlled Portions Population (N=5095)	All Clinical Trials Population (N=7253)
Avg duration of follow-up (weeks)	13.0	134.2	15.7	71.7	8.2	89.1	8.1	134.3	11.5	114.1
Frequency[b]										
Ustekinumab vs Placebo/Comparator[c]	0.4% vs 0.4%	2.5% vs 0.5%	0.0% vs 0.3%	1.4% vs 0.3%	1.5% vs 1.1%	7.2% vs 2.2%	0.5% vs 1.3%	5.6% vs 3.1%	0.6% vs 0.6%	3.9% vs 1.2%
Odds ratio (95% CI)	0.989 (0.331, 2.957)	-	-	-	1.412 (0.597, 3.337)	-	0.370 (0.082, 1.664)	-	1.011 (0.562, 1.818)	-
Seriousness/outcomes										
Was Serious	9 (0.4%)	90 (2.5%)	0 (0.0%)	14 (1.4%)	21 (1.5%)	132 (7.2%)	3 (0.5%)	46 (5.6%)	33 (0.6%)	282 (3.9%)
Resulted in Death	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	3 (<0.1%)
Recovered	9 (0.4%)	82 (2.3%)	0 (0.0%)	14 (1.4%)	21 (1.5%)	129 (7.1%)	3 (0.5%)	44 (5.3%)	33 (0.6%)	269 (3.7%)
Did not recover (Persisted)	0 (0.0%)	6 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	10 (0.1%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity										
Mild	0 (0.0%)	4 (0.1%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	4 (0.2%)	0 (0.0%)	1 (0.1%)	2 (<0.1%)	9 (0.1%)
Moderate	1 (<0.1%)	25 (0.7%)	0 (0.0%)	6 (0.6%)	10 (0.7%)	59 (3.2%)	2 (0.3%)	31 (3.8%)	13 (0.3%)	121 (1.7%)
Severe	8 (0.3%)	61 (1.7%)	0 (0.0%)	8 (0.8%)	9 (0.6%)	69 (3.8%)	1 (0.2%)	14 (1.7%)	18 (0.4%)	152 (2.1%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

a: Psoriasis studies include C0379T01, C0379T02, C0379T04, C0743T08, C0743T09, C0743T12, C0743T23, C0743T25, and JNS009-JPN-02. PsA studies include C0743T10, CNTO1275PsA3001, and CNTO1275PsA3002. Crohn's disease studies include C0379T07, C0743T26, CNTO1275CRD3001, CNTO1275CRD3002 and CNTO1275CRD3003 (Week 272 Database Lock). Ulcerative Colitis study includes CNTO1275UCO3001 (Induction Study and Maintenance Study through Week 220 Database Lock).

b: Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.

c: The denominators for the combined comparator groups are:
Psoriasis studies - Controlled Portions (N=1305), Psoriasis studies - All Clinical Trials (N=1305)
PsA studies - Controlled Portions (N=379), PsA studies - All Clinical Trials (N=379)
Crohn's studies - Controlled Portions (N=650), Crohn's studies - All Clinical Trials (N=650)
Ulcerative Colitis study - Controlled Portions (N=319), Ulcerative Colitis study - All Clinical Trials (N=319)
All studies - Controlled Portions (N=2653), All studies - All Clinical Trials (N=2653)

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Table SVII.2: Important Potential Risk - Mycobacterial and Salmonella Infections; Treated Subjects Across Indications

	Psoriasis Studies[a]		PsA Studies[a]		Crohn's Disease Studies[a]		Ulcerative Colitis Study[a]		All Studies[a]	
	Controlled Portions Population (N=2501)	All Clinical Trials Population (N=3740)	Controlled Portions Population (N=692)	All Clinical Trials Population (N=1018)	Controlled Portions Population (N=1387)	All Clinical Trials Population (N=1823)	Controlled Portions Population (N=641)	All Clinical Trials Population (N=826)	Controlled Portions Population (N=5221)	All Clinical Trials Population (N=7407)
Avg duration of follow-up (weeks)	13.0	131.5	15.7	71.7	8.2	89.1	8.1	134.3	11.5	113.1
Frequency[b]										
Ustekinumab vs Placebo/Comparator[c]	0.0% vs 0.0%	<0.1% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.1% vs 0.0%	0.0% vs 0.0%	0.2% vs 0.0%	0.0% vs 0.0%	0.1% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-	-	-	-	-
Seriousness/outcomes										
Was Serious	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (<0.1%)
Resulted in Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	1 (<0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	5 (0.1%)
Did not recover (Persisted)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity										
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (<0.1%)
Moderate	0 (0.0%)	1 (<0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	3 (<0.1%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (<0.1%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

a: Psoriasis studies include C0379T01, C0379T02, C0379T04, C0743T08, C0743T09, C0743T12, C0743T23, C0743T25, and JNS009-JPN-02. PsA studies include C0743T10, CNTO1275PsA3001, and CNTO1275PsA3002. Crohn's disease studies include C0379T07, C0743T26, CNTO1275CRD3001, CNTO1275CRD3002 and CNTO1275CRD3003 (Week 272 Database Lock). Ulcerative Colitis study includes CNTO1275UCO3001 (Induction Study and Maintenance Study through Week 220 Database Lock).

b: Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.

c: The denominators for the combined comparator groups are:
Psoriasis studies - Controlled Portions (N=1337), Psoriasis studies - All Clinical Trials (N=1337)
PsA studies - Controlled Portions (N=379), PsA studies - All Clinical Trials (N=379)
Crohn’s studies - Controlled Portions (N=650), Crohn’s studies - All Clinical Trials (N=650)
Ulcerative Colitis study - Controlled Portions (N=319), Ulcerative Colitis study - All Clinical Trials (N=319)
All studies - Controlled Portions (N=2685), All studies - All Clinical Trials (N=2685)

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Table SVII.3: Important Potential Risk - Serious Infections; Treated Subjects Across Pediatric Studies

	Pediatric Psoriasis Studies[a]		Pediatric Crohn's disease Studies[a]	All Pediatric Studies[a]
	All Randomized, Controlled Portions Blinded Trials Population (N=73)	All Clinical Trials Population (N=154)	All Clinical Trials Population (N=82)	All Clinical Trials Population (N=236)
Avg duration of follow-up (weeks)	12.3	68.5	80.2	72.6
Frequency[b]				
Ustekinumab vs Placebo/Comparator[c]	0.0% vs 0.0%	1.9% vs 0.0%	1.2% vs NA	1.7% vs 0.0%
Odds ratio (95% CI)	-	-	-	-
Seriousness/outcomes				
Was Serious	0 (0.0%)	3 (1.9%)	1 (1.2%)	4 (1.7%)
Resulted in Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	3 (1.9%)	1 (1.2%)	4 (1.7%)
Did not recover (Persisted)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity				
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	3 (1.9%)	0 (0.0%)	3 (1.3%)
Severe	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (0.4%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[a] Pediatric psoriasis studies include CNTO1275PSO3006 and CNTO1275PSO3013, Pediatric Crohn's disease studies include CNTO1275CRD1001 (Week 268 DBL) and CNTO1275CRD3004 (48 subjects ≥ 40 kg through Week M-44).
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are:
- Pediatric Psoriasis Studies - All Randomized, Controlled Portions Blinded Trials Population (N=37), All Clinical Trials Population (N=37).
- All Pediatric Studies - All Clinical Trials Population (N=37).

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Characterization of the Risk – Discussion:

The global safety database was searched for medically confirmed and medically unconfirmed cases that met reporting criteria for the Periodic Benefit Risk Evaluation Report (PBRER) and coded to relevant MedDRA SMQ(s) and/or PT(s). Based on the review of the data to date, no new safety information was identified for the important potential risk of 'Serious infections (including mycobacterial and salmonella infections).' No safety signal was identified.

The impact of serious infection on the individual patient may be significant. Patients with a history of latent TB require additional therapy prior to using STELARA. Patients with an active infection should discontinue use of STELARA until the infection is cleared. Patients who receive STELARA and develop an infection may have a more severe course. The risk of infection must be carefully weighed against the benefit conferred by use of ustekinumab.

Risk Factors and Risk Groups:

Serious infections

Risk factors for the development of serious infections include diabetes and other comorbidities and concomitant use of steroids, anti-TNFs, other immunosuppressants, or other biologics.

TB

The most common risk factors for the development of TB include conditions impairing the development of effective cell-mediated immunity to the infection (ie, advanced age, HIV infection), alcohol abuse, malignancy, corticosteroids or other immunosuppression, connective tissue disease, renal failure, diabetes, and pregnancy.

A risk factor for the development of TB is exposure to TB, and patients who were born or lived in countries considered by the World Health Organization to have a high TB burden (incidence: >300 TB cases/100,000 population/year) or have travelled to these locations may be at higher risk. Exposure in the health care setting or in high-density institutions (ie, prisons) may also put patients at higher risk of development of TB. The possibility of latent TB must be considered, especially in patients who have immigrated from or travelled to countries with a high prevalence of TB or had close contact with a person with active TB. In patients who are severely ill or immunocompromised, tuberculin tests may yield false negative results.

Non-TB mycobacterial (NTM) infections

A retrospective/prospective review performed in Australia, found that significant risks for non-HIV-associated pulmonary *Mycobacterium avium*/*Mycobacterium intracellulare* complex (MAC) disease included male sex (OR=2.1; 95% CI 1.0 to 4.5) and age >50 years (OR=26.5; 95% CI 10.9 to 67.3; O'Brien 2000). Similarly, in a US study (Cassidy 2009) including 933 patients with 1 or more NTM isolates, pulmonary disease prevalence was highest in persons aged >50 years (15.5 cases per 100,000 persons). In addition, chronic respiratory disease, especially chronic obstructive pulmonary disease treated with inhaled corticosteroid therapy is a strong risk factor for NTM pulmonary disease (Andrejak 2013). Prolonged occupational exposure to soil was an important risk factor for MAC infection in a US study (Reed 2006).

Salmonella

Factors that could increase risk of salmonella infection include activities that result in close contact with salmonella (eg, international travel, owning a pet bird or reptile) and health issues that weaken resistance to infection (eg, stomach or bowel disorders leading to use of antacids; recent antibiotic use; IBD; or impaired immunity from acquired immune deficiency syndrome, sickle cell disease, malaria, anti-rejection drugs taken after organ transplants, and corticosteroids) (Mayo Clinic 2014).

Preventability:

STELARA is contraindicated in patients with a clinically important, active infection (eg, active TB) (SmPC section 4.3 [Contraindications]). To prevent serious infections, it is recommended that live vaccines not be given concurrently with STELARA (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]).

Serious infections

Caution should be exercised when considering the use of STELARA in patients with a chronic infection or a history of recurrent infection (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 STELARA should not be administered until the infection resolves.

TB

STELARA must not be given to patients with active TB. STELARA should not be given to patients with latent TB unless treatment for latent TB is initiated prior to administering STELARA, including those patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving STELARA should be monitored closely for signs and symptoms of active TB during and after treatment.

NTM infections

Specific recommendations about the prevention of NTM infections are not available.

Salmonella

Salmonella infections may result from a variety of sources. Appropriate handling of raw poultry and eggs, avoidance of unpasteurized foods, and handwashing after handling food or animals that may carry salmonella are all means of reducing the risk of developing a salmonella infection.

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.

Further characterization of the incidence, risk factors, and potential relationships with the use of ustekinumab for serious infections is conducted through routine pharmacovigilance activities and registries.

Public Health Impact:

The potential public health impact is not known.

Annex 1 MedDRA Term:

SOC: Infections and infestations.

Important Potential Risk: Malignancy

Potential Mechanisms:

Scientific literature suggests that IL-12 can contribute to tumor immunosurveillance (Colombo 2002) and exogenous IL-12 can promote tumor-directed cytotoxic T cell responses in tumor vaccine strategies. In contrast, IL-23 has been reported to promote tumor growth in animal models. The preponderance of evidence from the published literature (knockout models where IL-23 is ablated) suggests that a risk for malignancy may actually be reduced in the setting of IL-23 inhibition. However, conflicting data from a limited number of studies in mouse models and from photocarcinogenicity experiments point to an increased risk of malignancy in IL-23p19-deficient mice exposed to UVB radiation. Studies in mice genetically deficient in IL-12, or mice treated with high doses of an anti-mouse IL-12/23p40 antibody, suggest that IL-12 contributes to immunity against certain mouse models of neoplasia (Rao 1997). Cárdenes (2010) described a 25-year old patient with IL-12Rβ1 deficiency who developed esophageal carcinoma. However, the contribution of endogenous human IL-12 or IL-23 to tumor immunosurveillance remains unclear.

Evidence Source(s) and Strength of Evidence:

There is a theoretical risk of malignancy associated with administration of STELARA based on scientific literature pertaining to inhibition of IL-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.

Because malignancies tend to take a long time to develop, long-term follow-up is most relevant. In psoriasis patients treated for up to 5 years of continuous STELARA therapy, the risk of malignancies other than non-melanoma skin cancer was not increased compared with the general US population. There was no evidence of an increased risk of malignancy through approximately 5 years of follow-up in CD patients and approximately 4 years of follow-up in UC patients treated with STELARA.

Long-term effects of STELARA on existing malignancies or in patients with a history of malignancy are not known. In light of the theoretical risk and the longer latency period for the development of malignancy, the topic warrants continued surveillance and malignancy is considered an important potential risk.

Characterization of the Risk – Data:

Table SVII.4: Important Potential Risk - Non-melanoma Skin Cancer; Treated Subjects Across Indications

	Psoriasis Studies[a]		PsA Studies[a]		Crohn's Disease Studies[a]		Ulcerative Colitis Study[a]		All Studies[a]	
	Controlled Portions Population (N=2501)	All Clinical Trials Population (N=3740)	Controlled Portions Population (N=692)	All Clinical Trials Population (N=1018)	Controlled Portions Population (N=1387)	All Clinical Trials Population (N=1823)	Controlled Portions Population (N=641)	All Clinical Trials Population (N=826)	Controlled Portions Population (N=5221)	All Clinical Trials Population (N=7407)
Avg duration of follow-up (weeks)	13.0	131.5	15.7	71.7	8.2	89.1	8.1	134.3	11.5	113.1
Frequency[b]										
Ustekinumab vs Placebo/Comparator[c]	0.2% vs 0.1%	1.3% vs 0.1%	0.1% vs 0.0%	0.4% vs 0.0%	0.0% vs 0.0%	0.7% vs 0.2%	0.0% vs 0.0%	0.8% vs 0.0%	0.1% vs 0.1%	1.0% vs 0.1%
Odds ratio (95% CI)	1.605 (0.324, 7.964)	-	-	-	-	-	-	-	1.801 (0.374, 8.675)	-
Seriousness/outcomes										
Was Serious	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.4%)	0 (0.0%)	4 (0.1%)
Resulted in Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	5 (0.2%)	41 (1.1%)	0 (0.0%)	3 (0.3%)	0 (0.0%)	12 (0.7%)	0 (0.0%)	7 (0.8%)	5 (0.1%)	63 (0.9%)
Did not recover (Persisted)	1 (<0.1%)	6 (0.2%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	2 (<0.1%)	8 (0.1%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity										
Mild	2 (0.1%)	24 (0.6%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	6 (0.3%)	0 (0.0%)	4 (0.5%)	2 (<0.1%)	36 (0.5%)
Moderate	3 (0.1%)	21 (0.6%)	1 (0.1%)	2 (0.2%)	0 (0.0%)	7 (0.4%)	0 (0.0%)	3 (0.4%)	4 (0.1%)	33 (0.4%)
Severe	1 (<0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (<0.1%)	2 (<0.1%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

a: Psoriasis studies include C0379T01, C0379T02, C0379T04, C0743T08, C0743T09, C0743T12, C0743T23, C0743T25, and JNS009-JPN-02. PsA studies include C0743T10, CNTO1275PsA3001, and CNTO1275PsA3002. Crohn's disease studies include C0379T07, C0743T26, CNTO1275CRD3001, CNTO1275CRD3002 and CNTO1275CRD3003 (Week 272 Database Lock). Ulcerative Colitis study includes CNTO1275UCO3001 (Induction Study and Maintenance Study through Week 220 Database Lock).

b: Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.

c: The denominators for the combined comparator groups are:
Psoriasis studies - Controlled Portions (N=1337), Psoriasis studies - All Clinical Trials (N=1337)
PsA studies - Controlled Portions (N=379), PsA studies - All Clinical Trials (N=379)
Crohn’s studies - Controlled Portions (N=650), Crohn’s studies - All Clinical Trials (N=650)
Ulcerative Colitis study - Controlled Portions (N=319), Ulcerative Colitis study - All Clinical Trials (N=319)
All studies - Controlled Portions (N=2685), All studies - All Clinical Trials (N=2685)

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Table SVII.5: Important Potential Risk - Malignancy other than Non-melanoma Skin Cancer; Treated Subjects Across Indications

	Psoriasis Studies[a]		PsA Studies[a]		Crohn's Disease Studies[a]		Ulcerative Colitis Study[a]		All Studies[a]	
	Controlled Portions Population (N=2501)	All Clinical Trials Population (N=3740)	Controlled Portions Population (N=692)	All Clinical Trials Population (N=1018)	Controlled Portions Population (N=1387)	All Clinical Trials Population (N=1823)	Controlled Portions Population (N=641)	All Clinical Trials Population (N=826)	Controlled Portions Population (N=5221)	All Clinical Trials Population (N=7407)
Avg duration of follow-up (weeks)	13.0	131.5	15.7	71.7	8.2	89.1	8.1	134.3	11.5	113.1
Frequency[b]										
Ustekinumab vs Placebo/Comparator[c]	0.1% vs 0.1%	1.5% vs 0.1%	0.0% vs 0.0%	0.3% vs 0.0%	0.0% vs 0.0%	0.7% vs 0.2%	0.0% vs 0.0%	0.8% vs 0.6%	0.1% vs <0.1%	1.1% vs 0.1%
Odds ratio (95% CI)	-	-	-	-	-	-	-	-	-	-
Seriousness/outcomes										
Was Serious	2 (0.1%)	50 (1.3%)	0 (0.0%)	3 (0.3%)	0 (0.0%)	8 (0.4%)	0 (0.0%)	6 (0.7%)	2 (<0.1%)	67 (0.9%)
Resulted in Death	0 (0.0%)	4 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.1%)
Recovered	0 (0.0%)	24 (0.6%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	6 (0.3%)	0 (0.0%)	7 (0.8%)	0 (0.0%)	39 (0.5%)
Did not recover (Persisted)	3 (0.1%)	28 (0.7%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	6 (0.3%)	0 (0.0%)	0 (0.0%)	3 (0.1%)	35 (0.5%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity										
Mild	1 (<0.1%)	9 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	1 (0.1%)	1 (<0.1%)	13 (0.2%)
Moderate	1 (<0.1%)	14 (0.4%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	7 (0.4%)	0 (0.0%)	1 (0.1%)	1 (<0.1%)	23 (0.3%)
Severe	1 (<0.1%)	33 (0.9%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	3 (0.2%)	0 (0.0%)	5 (0.6%)	1 (<0.1%)	42 (0.6%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

a: Psoriasis studies include C0379T01, C0379T02, C0379T04, C0743T08, C0743T09, C0743T12, C0743T23, C0743T25, and JNS009-JPN-02. PsA studies include C0743T10, CNTO1275PsA3001, and CNTO1275PsA3002. Crohn's disease studies include C0379T07, C0743T26, CNTO1275CRD3001, CNTO1275CRD3002 and CNTO1275CRD3003 (Week 272 Database Lock). Ulcerative Colitis study includes CNTO1275UCO3001 (Induction Study and Maintenance Study through Week 220 Database Lock).

b: Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.

c: The denominators for the combined comparator groups are:
Psoriasis studies - Controlled Portions (N=1337), Psoriasis studies - All Clinical Trials (N=1337)
PsA studies - Controlled Portions (N=379), PsA studies - All Clinical Trials (N=379)
Crohn’s studies - Controlled Portions (N=650), Crohn’s studies - All Clinical Trials (N=650)
Ulcerative Colitis study - Controlled Portions (N=319), Ulcerative Colitis study - All Clinical Trials (N=319)
All studies - Controlled Portions (N=2685), All studies - All Clinical Trials (N=2685)

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Characterization of the Risk – Discussion:

The global safety database was searched for medically confirmed and medically unconfirmed cases that met reporting criteria for the PBRER and coded to relevant MedDRA SMQ(s) and/or PT(s). Based on the review of the data to date, no new safety information was identified for the important potential risk of 'Malignancy.' No safety signal was identified. As noted above, the incidence of malignancy in ustekinumab clinical trials was consistent with that in the general population.

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving STELARA. Thus, caution should be exercised when considering the use of STELARA in these patients (SmPC section 4.4 [Special Warnings and Precautions of Use]).

The impact of malignancy on the individual patient may be very significant. Patients may potentially have a higher risk of developing malignancies due to use of an immunomodulating agent such as ustekinumab. This important potential risk needs to be carefully weighed against the benefit conferred by use of ustekinumab.

Risk Factors and Risk Groups:

Among psoriasis patients, increased risk of solid cancers appears to be related to alcohol drinking and cigarette smoking. In addition, exposure to PUVA and immunosuppressants, including cyclosporin and possibly MTX, has been associated with squamous cell carcinoma in psoriasis patients (Pouplard 2013). 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:

Predictability and preventability of the development of malignancy is not known. Protection from UV exposure, either solar or from tanning beds may decrease the risk of an individual developing a cutaneous malignancy. As indicated in SmPC section 4.4 (Special Warnings and Precautions of Use), caution should be exercised when considering the use of STELARA 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 (SmPC section 4.4 [Special Warnings and Precautions of Use]).

No testing is available to identify patients at risk for cutaneous malignancy.

Impact on the Risk-Benefit Balance of the Product:

Although malignancies have been reported in patients treated with ustekinumab in clinical trials and in the postmarketing setting, 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 and registries.

Public Health Impact:

The potential public health impact is not known.

Annex 1 MedDRA Term:

SMQ: Malignant tumours (narrow).

Important Potential Risk: Cardiovascular Events

Potential Mechanisms:

Patients with severe psoriasis are more likely to demonstrate CV risk factors such as obesity, diabetes, and hypertension when compared with those with no or mild psoriasis (Neimann 2006). The greatest risk of myocardial infarction (MI) is found in young patients with severe psoriasis (Gelfand 2006). As in psoriasis, patients with PsA are reported to be at increased risk for occlusive vascular diseases, including MI and stroke (Husted 2011; Tobin 2010; Li 2012; Gladman 2009a). The potential mechanistic link between psoriasis and CV events, if any, is unclear.

Subjects with CD and UC had an overall lower CV risk, based upon baseline CV risk factors, than the psoriasis and PsA populations.

Evidence Source(s) and Strength of Evidence:

The risk of developing CV events in subjects on anti-IL-12/23p40 therapy such as STELARA is currently unknown.

A numeric imbalance in rates of investigator-reported major adverse cardiovascular events (MACE) was observed between ustekinumab- and placebo-treated subjects in the controlled portions of Phase 2 and Phase 3 trials in psoriasis, resulting predominantly from an imbalance in event rates from a smaller Phase 2 trial. Additional analyses performed internally by the MAH show that the overall rates of MI and stroke with up to 5 years of treatment with STELARA in psoriasis patients are comparable with expected rates in either the general population or in the psoriasis population, and comparable to rates in trials of other biologics. Through approximately 5 years of follow-up in CD clinical trials and approximately 4 years of follow-up in UC clinical trials, the incidence of serious MACE was low in ustekinumab-treated subjects and placebo-treated subjects, with no consistent evidence that ustekinumab increases cardiovascular risk. Across indications, analysis of MACE in controlled portions of the pooled clinical trial data does not currently suggest a significant increased risk of MACE in subjects treated with ustekinumab.

In summary, the totality of the currently available data does not suggest that ustekinumab increases the risk of MACE. However, in light of the imbalance of CV events in the short-term, placebo-controlled portions of the psoriasis clinical trials and the known increased risk of these events in the psoriasis and PsA populations, CV events are considered an important potential risk for ustekinumab.

Characterization of the Risk – Data:

Table SVII.6: Important Potential Risk - Cardiovascular Events*; Treated Subjects Across Indications

	Psoriasis Studies[a]		PsA Studies[a]		Crohn's Disease Studies[a]		Ulcerative Colitis Study[a]		All Studies[a]	
	Controlled Portions Population (N=2501)	All Clinical Trials Population (N=3740)	Controlled Portions Population (N=692)	All Clinical Trials Population (N=1018)	Controlled Portions Population (N=1387)	All Clinical Trials Population (N=1823)	Controlled Portions Population (N=641)	All Clinical Trials Population (N=826)	Controlled Portions Population (N=5221)	All Clinical Trials Population (N=7407)
Avg duration of follow-up (weeks)	13.0	131.5	15.7	71.7	8.2	89.1	8.1	134.3	11.5	113.1
Frequency[b]										
Ustekinumab vs Placebo/Comparator[c]	0.2% vs 0.0%	1.0% vs 0.1%	0.0% vs 0.3%	1.0% vs 0.3%	0.0% vs 0.0%	0.4% vs 0.2%	0.0% vs 0.3%	0.6% vs 0.3%	0.1% vs 0.1%	0.8% vs 0.1%
Odds ratio (95% CI)	-	-	-	-	-	-	-	-	1.286 (0.249, 6.631)	-
Seriousness/outcomes										
Was Serious	5 (0.2%)	38 (1.0%)	0 (0.0%)	10 (1.0%)	0 (0.0%)	8 (0.4%)	0 (0.0%)	5 (0.6%)	5 (0.1%)	61 (0.8%)
Resulted in Death	1 (<0.1%)	6 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.2%)	0 (0.0%)	2 (0.2%)	1 (<0.1%)	11 (0.1%)
Recovered	4 (0.2%)	31 (0.8%)	0 (0.0%)	7 (0.7%)	0 (0.0%)	5 (0.3%)	0 (0.0%)	3 (0.4%)	4 (0.1%)	46 (0.6%)
Did not recover (Persisted)	0 (0.0%)	2 (0.1%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.1%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (<0.1%)
Severity										
Mild	0 (0.0%)	3 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (<0.1%)
Moderate	0 (0.0%)	9 (0.2%)	0 (0.0%)	4 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (0.2%)
Severe	5 (0.2%)	27 (0.7%)	0 (0.0%)	6 (0.6%)	0 (0.0%)	8 (0.4%)	0 (0.0%)	5 (0.6%)	5 (0.1%)	46 (0.6%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

*: For CNTO1275CRD3003 and CNTO1275UCO3001, events are viewed by clinical. For the rest of completed studies, events were adjudicated by an independent committee.

a: Psoriasis studies include C0379T01, C0379T02, C0379T04, C0743T08, C0743T09, C0743T12, C0743T23, C0743T25, and JNS009-JPN-02. PsA studies include C0743T10, CNTO1275PsA3001, and CNTO1275PsA3002. Crohn's disease studies include C0379T07, C0743T26, CNTO1275CRD3001, CNTO1275CRD3002 and CNTO1275CRD3003 (Week 272 Database Lock). Ulcerative Colitis study includes CNTO1275UCO3001 (Induction Study and Maintenance Study through Week 220 Database Lock).

b: Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.

c: The denominators for the combined comparator groups are:
Psoriasis studies - Controlled Portions (N=1337), Psoriasis studies - All Clinical Trials (N=1337)
PsA studies - Controlled Portions (N=379), PsA studies - All Clinical Trials (N=379)
Crohn’s studies - Controlled Portions (N=650), Crohn’s studies - All Clinical Trials (N=650)
Ulcerative Colitis study - Controlled Portions (N=319), Ulcerative Colitis study - All Clinical Trials (N=319)
All studies - Controlled Portions (N=2685), All studies - All Clinical Trials (N=2685)

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Characterization of the Risk – Discussion:

The global safety database was searched for medically confirmed and medically unconfirmed cases that met reporting criteria for the PBRER and coded to relevant MedDRA SMQ(s) and/or PT(s). Based on the review of the data to date, no new safety information was identified for the important potential risk of 'Cardiovascular events.' No safety signal was identified.

There is evidence for an increased background risk of CV disease in patients with psoriasis and IBD, and patients may experience debilitating MI, stroke, or death. Patients are not considered at further CV risk from use of STELARA beyond that related to the psoriasis or IBD population risk. Patients with psoriasis and IBD require vigilance and adequate treatment of CV risk factors including hypertension, hypercholesterolemia, and diabetes. The impact of MACE on the individual patient is potentially significant. Major adverse cardiovascular events may result in fatal outcome.

Risk Factors and Risk Groups:

Risk factors for the development of CV disease are well known and include hypertension, hypercholesterolemia, diabetes, smoking, age, male sex, obesity, and family history. The PsA, psoriasis, and CD populations share certain risk factors, such as increased CV risk, increased body weight, and increased BMI (Augustin 2010; Bostoen 2014; Román 2011; Kristensen 2013; Dregan 2014).

Preventability:

The preventability of CV disease is based upon the modification of known risk factors. A relationship between CV events and STELARA has not been established. The effects of STELARA on hypertension, diabetes, glycemic control, and weight were evaluated in the Phase 3 psoriasis and PsA trials; no apparent impact was found.

Impact on the Risk-Benefit Balance of the Product:

Although MACE have been reported in patients treated with ustekinumab in clinical trials and in the postmarketing setting, the available cumulative information does not provide compelling evidence for an increased risk of MACE in patients treated with ustekinumab. Therefore, no significant negative impact on the risk-benefit balance of the product is expected.

Public Health Impact:

The potential public health impact is not known.

Annex 1 MedDRA Term:

SOC: Cardiac disorders.

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 STELARA could cause depression is not known.

Evidence Source(s) and Strength of Evidence:

Psoriasis patients can have an increased risk for depression and, in rare cases, suicide. Depression has been identified as an ADR for STELARA (SmPC section 4.8 [Undesirable Effects] and PL section 4) based on a safety signal identified in the placebo-controlled period from the Phase 2 and Phase 3 psoriasis clinical trials. The incidence of serious depression including suicidality across indications remains low.

The available safety data from clinical studies and postmarketing experience have not identified a safety signal of suicidal ideation or suicidal attempt (including completed suicide). However, based on the severity of these events, serious depression including suicidality is considered an important potential risk for STELARA.

Characterization of the Risk – Data:

Table SVII.7: Important Potential Risk - Serious Depression (Including Suicidality); Treated Subjects Across Indications

	Psoriasis Studies[a]		PsA Studies[a]		Crohn's Disease Studies[a]		Ulcerative Colitis Study[a]		All Studies[a]	
	Controlled Portions Population (N=2501)	All Clinical Trials Population (N=3740)	Controlled Portions Population (N=692)	All Clinical Trials Population (N=1018)	Controlled Portions Population (N=1387)	All Clinical Trials Population (N=1823)	Controlled Portions Population (N=641)	All Clinical Trials Population (N=826)	Controlled Portions Population (N=5221)	All Clinical Trials Population (N=7407)
Avg duration of follow-up (weeks)	13.0	131.5	15.7	71.7	8.2	89.1	8.1	134.3	11.5	113.1
Frequency[b]										
Ustekinumab vs Placebo/Comparator[c]	0.0% vs 0.0%	0.2% vs 0.0%	0.1% vs 0.3%	0.4% vs 0.5%	0.1% vs 0.0%	0.4% vs 0.2%	0.0% vs 0.0%	0.1% vs 0.0%	0.1% vs <0.1%	0.3% vs 0.1%
Odds ratio (95% CI)	-	-	-	-	-	-	-	-	-	-
Seriousness/outcomes										
Was Serious	0 (0.0%)	7 (0.2%)	1 (0.1%)	4 (0.4%)	2 (0.1%)	8 (0.4%)	0 (0.0%)	1 (0.1%)	3 (0.1%)	20 (0.3%)
Resulted in Death	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (<0.1%)
Recovered	0 (0.0%)	3 (0.1%)	1 (0.1%)	3 (0.3%)	2 (0.1%)	7 (0.4%)	0 (0.0%)	1 (0.1%)	3 (0.1%)	14 (0.2%)
Did not recover (Persisted)	0 (0.0%)	2 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (<0.1%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity										
Mild	0 (0.0%)	1 (<0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (<0.1%)	2 (<0.1%)
Moderate	0 (0.0%)	3 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	3 (0.2%)	0 (0.0%)	0 (0.0%)	2 (<0.1%)	7 (0.1%)
Severe	0 (0.0%)	3 (0.1%)	0 (0.0%)	3 (0.3%)	0 (0.0%)	4 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	11 (0.1%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

a: Psoriasis studies include C0379T01, C0379T02, C0379T04, C0743T08, C0743T09, C0743T12, C0743T23, C0743T25, and JNS009-JPN-02. PsA studies include C0743T10, CNTO1275PsA3001, and CNTO1275PsA3002. Crohn's disease studies include C0379T07, C0743T26, CNTO1275CRD3001, CNTO1275CRD3002 and CNTO1275CRD3003 (Week 272 Database Lock). Ulcerative Colitis study includes CNTO1275UCO3001 (Induction Study and Maintenance Study through Week 220 Database Lock).

b: Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.

c: The denominators for the combined comparator groups are:
Psoriasis studies - Controlled Portions (N=1337), Psoriasis studies - All Clinical Trials (N=1337)
PsA studies - Controlled Portions (N=379), PsA studies - All Clinical Trials (N=379)
Crohn’s studies - Controlled Portions (N=650), Crohn’s studies - All Clinical Trials (N=650)
Ulcerative Colitis study - Controlled Portions (N=319), Ulcerative Colitis study - All Clinical Trials (N=319)
All studies - Controlled Portions (N=2685), All studies - All Clinical Trials (N=2685)

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Characterization of the Risk – Discussion:

The global safety database was searched for medically confirmed and medically unconfirmed cases that met reporting criteria for the PBRER and coded to relevant MedDRA SMQ(s) and/or PT(s). Based on the review of the data to date, no new safety information was identified for the important potential risk of 'Serious depression including suicidality.' No safety signal was identified.

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.

Risk Factors and Risk Groups:

Risk factors for depression include older age and associated neurological conditions; uncontrolled, poorly treated psoriasis; recent childbirth; stressful life events; a personal or family history of depression; and selected medical comorbid conditions including psoriatic conditions and IBD. Suicide rates are twice as high in families of suicide victims (Fancher 2007).

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 and in the postmarketing setting, 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 and registries.

Public Health Impact:

The potential public health impact is not known.

Annex 1 MedDRA Term:

SMQ: Depression and suicide/self-injury (broad).

Important Potential Risk: Venous Thromboembolism

Potential Mechanisms:

Currently, there is no known mechanism by which STELARA could induce or exacerbate VTE. The available literature shows that IL-12 and IL-23 are not implicated in the process of venous thrombosis.

However, patients with IBD are at higher risk of venous thrombosis. Venous thromboembolism in patients with IBD is a multifactorial event that involves both hereditary (factor V Leiden mutation, G20210A mutation of the prothrombin gene, and homozygous C677T mutation in the methylenetetrahydrofolate reductase gene) and acquired factors (dehydration, indwelling catheters, prolonged immobilization, hyperhomocysteinemia, surgical interventions, active disease with a high inflammatory burden, hospitalization, colonic localization, recent surgery, oral contraceptive use, etc).

The pathogenesis of thrombosis in IBD is complex and not fully known. In patients with IBD, several mechanisms triggered by active inflammation may contribute to a higher prothrombotic state. These mechanisms include:

- Increased plasma levels of recognized risk factors for thrombosis (eg, TNFα, IL-6, and IL-8 levels, several of which are also considered to be acute-phase reactant) and decreased levels of natural anticoagulants
- Reduced fibrinolytic activity
- Endothelial abnormalities that are mainly represented by the downregulation of the anticoagulant thrombomodulin and endothelial protein C receptor, which in turn affects the conversion of protein C into its activated form
- Abnormalities of platelets, such as thrombocytosis and increased activation and aggregation (Papa 2014).

STELARA inhibits IL-12/23 and the inhibition of IL-23 is associated with reduced plasma levels of the pro-inflammatory cytokines (TNFα, IL-6, and IL-8) that have been implicated in thrombogenesis. Therefore, currently there is no evidence to suggest biologic plausibility for the inhibition of IL-12/23 contributing to the development of thrombosis.

Evidence Source(s) and Strength of Evidence:

Patients with IBD can have an increased risk for blood clots in veins due to their underlying condition and other risk factors (dehydration, use of catheters, prolonged immobilization, hospitalization, surgical interventions, oral contraceptive use, etc).

Venous thromboembolism was originally identified as an important potential risk based on data collected through 44 weeks of treatment in the ustekinumab CD clinical trials. Through approximately 5 years of follow-up in CD clinical trials and approximately 4 years of follow-up in UC clinical trials, while there is a slight imbalance across treatment groups in the reporting of all vascular thrombotic events, the overall incidences per 100 subject-years (~0.1 [~1%]) observed among STELARA-treated subjects in both the CD and UC populations are within the range of 1% to 8% reported in the IBD literature (Alkim 2017; Danese 2007; Nguyen 2014).

Overall, safety results from the CD clinical trials through Week 272, UC clinical trials through Week 220, and clinical trials conducted for other indications, as well as cumulative postmarketing data, do not indicate an increased rate with ustekinumab treatment.

Characterization of the Risk – Data:

Table SVII.8: Important Potential Risk - Number of Subjects with Treatment Emergent Venous Thromboembolism; Treated Subjects Across Indications

	Psoriasis Studies[a]		PsA Studies[a]		Crohn's Disease Studies[a]		Ulcerative Colitis Study[a]		All Studies[a]	
	Controlled Portions Population (N=2501)	All Clinical Trials Population (N=3740)	Controlled Portions Population (N=692)	All Clinical Trials Population (N=1018)	Controlled Portions Population (N=1387)	All Clinical Trials Population (N=1823)	Controlled Portions Population (N=641)	All Clinical Trials Population (N=826)	Controlled Portions Population (N=5221)	All Clinical Trials Population (N=7407)
Avg duration of follow-up (weeks)	13.0	131.5	15.7	71.7	8.2	89.1	8.1	134.3	11.5	113.1
Frequency[b]										
Ustekinumab vs Placebo/Comparator[c]	<0.1% vs 0.0%	0.4% vs 0.0%	0.0% vs 0.0%	0.1% vs 0.0%	0.2% vs 0.2%	0.9% vs 0.5%	0.3% vs 0.0%	1.0% vs 0.6%	0.1% vs <0.1%	0.6% vs 0.2%
Odds ratio (95% CI)	-	-	-	-	-	-	-	-	3.086 (0.372, 25.629)	-
Seriousness/outcomes										
Was Serious	0 (0.0%)	7 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (0.4%)	2 (0.3%)	3 (0.4%)	2 (<0.1%)	18 (0.2%)
Resulted in Death	0 (0.0%)	1 (<0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (<0.1%)
Recovered	1 (<0.1%)	13 (0.3%)	0 (0.0%)	1 (0.1%)	3 (0.2%)	12 (0.7%)	2 (0.3%)	8 (1.0%)	6 (0.1%)	34 (0.5%)
Did not recover (Persisted)	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (0.1%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity										
Mild	0 (0.0%)	3 (0.1%)	0 (0.0%)	0 (0.0%)	3 (0.2%)	5 (0.3%)	0 (0.0%)	3 (0.4%)	3 (0.1%)	11 (0.1%)
Moderate	1 (<0.1%)	10 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (0.3%)	1 (0.2%)	3 (0.4%)	2 (<0.1%)	19 (0.3%)
Severe	0 (0.0%)	3 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	6 (0.3%)	1 (0.2%)	2 (0.2%)	1 (<0.1%)	12 (0.2%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

a: Psoriasis studies include C0379T01, C0379T02, C0379T04, C0743T08, C0743T09, C0743T12, C0743T23, C0743T25, and JNS009-JPN-02. PsA studies include C0743T10, CNTO1275PsA3001, and CNTO1275PsA3002. Crohn's disease studies include C0379T07, C0743T26, CNTO1275CRD3001, CNTO1275CRD3002 and CNTO1275CRD3003 (Week 272 Database Lock). Ulcerative Colitis study includes CNTO1275UCO3001 (Induction Study and Maintenance Study through Week 220 Database Lock).

b: Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.

c: The denominators for the combined comparator groups are:
Psoriasis studies - Controlled Portions (N=1337), Psoriasis studies - All Clinical Trials (N=1337)
PsA studies - Controlled Portions (N=379), PsA studies - All Clinical Trials (N=379)
Crohn’s studies - Controlled Portions (N=650), Crohn’s studies - All Clinical Trials (N=650)
Ulcerative Colitis study - Controlled Portions (N=319), Ulcerative Colitis study - All Clinical Trials (N=319)
All studies - Controlled Portions (N=2685), All studies - All Clinical Trials (N=2685)

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Characterization of the Risk – Discussion:

The global safety database was searched for medically confirmed and medically unconfirmed cases that met reporting criteria for the PBRER and coded to relevant MedDRA SMQ(s) and/or PT(s). Based on the review of the data to date, no new safety information was identified for the important potential risk of 'Venous thromboembolism.' No safety signal was identified.

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 (Nguyen 2014). Patients with IBD require vigilance in adequate treatment of VTE risk factors.

Risk Factors and Risk Groups:

Patients suffering from IBD, namely CD and UC, are more prone to thromboembolic complications compared with the general population (Zezos 2014).

A study of IBD patients conducted in the UK reported that there was increased risk of VTE during disease flares and chronic activity (Grainge 2010). In a Danish population study that included children and adults, the highest risk of VTE was in the 0 to 20 years age group with an HR of 6.6 (95% CI 3.3 to 13.2) compared with 1.6 (95% CI 1.5 to 1.8) for the ≥60 years age group (Kappelman 2011). The risk has also been reported to be greater for males (incidence rate of 1.34 per 1,000 PY) than for females (incidence rate of 0.73 per 1,000 PY). Smoking and the need for steroid treatment have also been shown to be risk factors for VTE with ORs of 3.46 (95% CI 1.14 to 10.5) and 2.97 (95% CI 0.99 to 8.92), respectively (Vegh 2015).

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 providing adequate hydration, effective anti-inflammatory treatment, early mobilization after surgery, graduated compression stockings or pneumatic devices, limited and rational use of venous catheters, weight loss, alternative methods of contraception, etc.

Impact on the Risk-Benefit Balance of the Product:

Although VTE has been reported in patients treated with ustekinumab in clinical trials and in the postmarketing setting, 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, clinical trials, and an epidemiological study.

Public Health Impact:

The potential public health impact is not known.

Annex 1 MedDRA Term:

SMQ: Embolic and thrombotic events, venous (broad).

SVII.3.2. Presentation of the Missing Information

Missing information: Long-term safety in pediatric psoriasis patients 6 years and older
Evidence source: A relatively small number of pediatric subjects ≥6 to <18 years of age (71 male and 83 female) were exposed to ustekinumab in the pediatric psoriasis clinical trials. Trials CNTO1275PSO3006 and CNTO1275PSO3013 investigated the use of ustekinumab in pediatric psoriasis patients through 60 weeks and 176 weeks, respectively.
Population in need of further characterization: Pediatric psoriasis patients ≥6 years of age who have been treated with STELARA long-term. A postauthorization safety study (PASS), CNTO1275PSO4056 (Pediatric Psoriasis Registry) to characterize the long-term safety profile of STELARA in pediatric patients ≥6 years of age is ongoing.

Missing information: Long-term impact on growth and development in pediatric psoriasis patients 6 years and older
Evidence source: A relatively small number of pediatric subjects ≥6 to <18 years of age (71 male and 83 female) were exposed to ustekinumab in the pediatric psoriasis clinical trials. Trials CNTO1275PSO3006 and CNTO1275PSO3013 investigated the use of ustekinumab in pediatric psoriasis patients through 60 weeks and 176 weeks, respectively.
Population in need of further characterization: Pediatric psoriasis patients ≥6 years of age who have been treated with STELARA long-term. A PASS, CNTO1275PSO4056 (Pediatric Psoriasis Registry) to characterize the long-term safety profile of STELARA in pediatric patients ≥6 years of age is ongoing.

Missing information: Long-term safety in adult patients with moderately to severely active Crohn's disease
Evidence source: Trials CNTO1275CRD3001, CNTO1275CRD3002, and CNTO1275CRD3003 investigated the use of ustekinumab in adult CD from the first dose of ustekinumab through Week 272. RRA-20745, an observational PASS, monitored the long-term safety profile of ustekinumab in adult patients with moderately to severely active CD.
Population in need of further characterization: Adults with moderately to severely active CD who have been treated with STELARA long-term. A PASS using Swedish Nationwide Healthcare Registers and the independent Swedish National Quality Register for Inflammatory Bowel Disease (SWIBREG; PCSIMM002807) to characterize the long-term safety profile of STELARA in adult patients with moderately to severely active CD is ongoing.

Missing information: Long-term safety in adult patients with moderately to severely active ulcerative colitis
Evidence source: Trial CNTO1275UCO3001 investigated the use of ustekinumab in adult UC from the first dose of ustekinumab through Week 220.
Population in need of further characterization: Adults with moderately to severely active UC who have been treated with STELARA long-term. A PASS using Swedish Nationwide Healthcare Registers and the independent Swedish National Quality Register for Inflammatory Bowel Disease (SWIBREG; PCSIMM002807) and a PASS using the independent French Nationwide Claims Database (SNDS; PCSIMM002659) to characterize the long-term safety of ustekinumab in adult patients with moderately to severely active UC are ongoing.

Missing information: Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease
Evidence source: A relatively small number of pediatric subjects aged 2 to <18 years and weighing 40 kg and above (40 male and 42 female) were exposed to ustekinumab in the pediatric CD clinical trials. Trials CNTO1275CRD1001 and CNTO1275CRD3004 investigated the use of ustekinumab in pediatric CD patients through Week 240 and through Week 52, respectively.
Population in need of further characterization: Pediatric patients with moderately to severely active CD and weighing 40 kg and above with long-term exposure to STELARA. An LTE study of ustekinumab in pediatric clinical study participants (2 to <18 years of age; CNTO1275ISD3001 [UNITED] LTE) to collect long-term safety data in pediatric patients who receive SC ustekinumab for at least 1 year after participating in a primary pediatric ustekinumab trial (CNTO1275CRD1001, CNTO1275PUC3001, CNTO1275CRD3004, and CNTO1275JPA3001) is ongoing.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: 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 adult patients with moderately to severely active ulcerative colitis
	Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Adverse Reaction Follow-up Questionnaires	
Safety Concern	**Purpose/Description**
Serious infections (including mycobacterial and salmonella infections)	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)
Malignancy	Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Malignancies (including Lymphoma, Second and Secondary Malignancies)
Cardiovascular events	Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Cardiovascular Events
Venous thromboembolism	Topic of Interest Questionnaire (TOIQ) for Venous Thromboembolism (VTE)

Other Forms of Routine Pharmacovigilance Activities		
Activity	**Objective/Description**	**Milestones**
Not applicable		

III.2. Additional Pharmacovigilance Activities

Study name and title	CNTO1275PSO4056 (Pediatric Psoriasis Registry): An observational postauthorization safety study of ustekinumab in the treatment of pediatric patients aged 6 years and older with moderate to severe plaque psoriasis
Rationale and study objectives	The objective of this study is to confirm the long-term safety profile of STELARA use in pediatric patients 6 years and older and to explore any potential effect on growth and development in pediatric patients 6 years and older in-line with the consideration in the STELARA PIP.
Safety concern(s) addressed	• 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
Study design	Prospective, observational, international, multicenter registry study.
Study population	Patients with psoriasis who are 6 years or older and meet all eligibility criteria.

Milestones	Protocol submission: 21 December 2015 Start of data collection: 25 October 2017 End of data collection: 31 August 2032 Final report: 31 March 2033
Study name and title	An observational postauthorization safety study to describe the safety of ustekinumab and other biologic treatments in a cohort of patients with ulcerative colitis or Crohn's disease using compulsory Swedish Nationwide Healthcare Registers and the independent Swedish National Quality Register for Inflammatory Bowel Disease (SWIBREG; PCSIMM002807).
Rationale and study objectives	The objective of this study is to monitor the long-term safety profile of ustekinumab in adult patients with moderately to severely active UC or CD.
Safety concern(s) addressed	• Venous thromboembolism • Malignancy • Cardiovascular events (MACE only) • Serious infections (including mycobacterial and salmonella infections) • Long-term safety in adult patients with moderately to severely active ulcerative colitis • Long-term safety in adult patients with moderately to severely active Crohn's disease
Study design	Observational cohort study.
Study population	UC and CD patients who receive ustekinumab treatment or other biologic treatments within routine clinical practice.
Milestones	Protocol submission: 23 June 2020 Start of data collection: 30 November 2022 End of data collection: 30 November 2027 Final report: 31 December 2028
Study name and title	An observational postauthorization safety study to describe the safety of ustekinumab and other treatments of ulcerative colitis in a cohort of patients with ulcerative colitis using the independent French Nationwide Claims Database (SNDS; PCSIMM002659)
Rationale and study objectives	The objective of this study is to monitor the long-term safety profile of ustekinumab in adult patients with moderately to severely active UC.
Safety concern(s) addressed	• Venous thromboembolism • Malignancy • Cardiovascular events (MACE only) • Serious infections (including mycobacterial and salmonella infections) • Long-term safety in adult patients with moderately to severely active ulcerative colitis
Study design	Observational cohort study.

Study population	Patients who receive ustekinumab treatment or other UC treatments within routine clinical practice.
Milestones	Protocol submission: 23 June 2020 Start of data collection: 31 December 2022 End of data collection: 31 December 2026 Final report: 31 December 2027
Study name and title	CNTO1275ISD3001 (UNITED) LTE: A Phase 3, multicenter, open-label, basket, long-term extension study of ustekinumab in pediatric clinical study participants (2 to <18 years of age)
Rationale and study objectives	The objective of this study is to collect long-term safety data in pediatric patients 2 to <18 years of age who receive SC ustekinumab for at least 1 year after participating in a primary pediatric ustekinumab trial (CNTO1275CRD1001, CNTO1275PUC3001, CNTO1275CRD3004, and CNTO1275JPA3001).
Safety concern(s) addressed	• Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease
Study design	Open-label, basket, multicenter, LTE study.
Study population	Pediatric patients 2 to <18 years of age who received SC ustekinumab in a primary pediatric ustekinumab trial and who, in the opinion of the investigator, will continue to benefit from ustekinumab therapy.
Milestones	Protocol submission: July 2024 Start of data collection: 18 October 2021 End of data collection: 31 July 2029 Final report: 31 January 2030

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
CNTO1275PSO4056 (Pediatric Psoriasis Registry): An observational postauthorization safety study of ustekinumab in the treatment of pediatric patients aged 6 years and older with moderate to severe plaque psoriasis Ongoing	To confirm the long-term safety profile of STELARA use in pediatric patients 6 years and older and to explore any potential effect on growth and development in pediatric patients 6 years and older in-line with the consideration in the STELARA PIP.	• 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	Protocol submission	21 December 2015
			Start of data collection	25 October 2017
			End of data collection	31 August 2032
			Final report	31 March 2033
An observational postauthorization safety study to describe the safety of ustekinumab and other biologic treatments in a cohort of patients with ulcerative colitis or Crohn's disease using compulsory Swedish Nationwide Healthcare Registers and the independent Swedish National Quality Register for Inflammatory Bowel Disease (SWIBREG; PCSIMM002807) Ongoing	To monitor the long-term safety profile of ustekinumab in adult patients with moderately to severely active UC or CD.	• Venous thromboembolism • Malignancy • Cardiovascular events (MACE only) • Serious infections (including mycobacterial and salmonella infections) • Long-term safety in adult patients with moderately to severely active ulcerative colitis • Long-term safety in adult patients with moderately to severely active Crohn's disease	Protocol submission	23 June 2020
			Start of data collection	30 November 2022
			End of data collection	30 November 2027
			Final report	31 December 2028

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
An observational postauthorization safety study to describe the safety of ustekinumab and other treatments of ulcerative colitis in a cohort of patients with ulcerative colitis using the independent French Nationwide Claims Database (SNDS; PCSIMM002659) Ongoing	To monitor the long-term safety profile of ustekinumab in adult patients with moderately to severely active UC.	• Venous thromboembolism • Malignancy • Cardiovascular events (MACE only) • Serious infections (including mycobacterial and salmonella infections) • Long-term safety in adult patients with moderately to severely active ulcerative colitis	Protocol submission	23 June 2020
			Start of data collection	31 December 2022
			End of data collection	31 December 2026
			Final report	31 December 2027
CNTO1275ISD3001 (UNITED) LTE: A Phase 3, multicenter, open-label, basket, long-term extension study of ustekinumab in pediatric clinical study participants (2 to <18 years of age) Ongoing	To collect long-term safety data in pediatric patients 2 to <18 years of age who receive SC ustekinumab for at least 1 year after participating in a primary pediatric ustekinumab trial (CNTO1275CRD1001, CNTO1275PUC3001, CNTO1275CRD3004, and CNTO1275JPA3001).	• Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease	Protocol submission	July 2024
			Start of data collection	18 October 2021
			End of data collection	31 July 2029
			Final report	31 January 2030

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Not applicable.

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Serious infections (including mycobacterial and salmonella infections)	**Routine risk communication:** SmPC sections 4.3 (Contraindications), 4.4 (Special Warnings and Precautions for Use), 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction), 4.6 (Fertility, Pregnancy and Lactation), and 4.8 (Undesirable Effects) PL sections 2 and 4 **Routine risk minimization 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 STELARA. • Recommendation to monitor patients for signs and symptoms of active TB during and after STELARA 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 [Interaction with Other Medicinal Products and Other Forms of Interaction]). 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. • 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.

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
	PL section 4 • Guidance for patients who develop signs of an infection or have open cuts or sores while using STELARA. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Malignancy	**Routine risk communication:** SmPC sections 4.4 (Special Warnings and Precautions for Use) and 4.8 (Undesirable Effects) PL section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC section 4.4 (Special Warnings and Precautions for Use) • Guidance for monitoring patients for the appearance of skin cancer. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Cardiovascular events	**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.
Serious depression including suicidality	**Routine risk communication:** SmPC section 4.8 (Undesirable Effects) PL section 4 **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.

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Venous thromboembolism	**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.
Long-term safety in pediatric psoriasis patients 6 years and older	**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.
Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	**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.
Long-term safety in adult patients 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.

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Long-term safety in adult patients with moderately to severely active ulcerative colitis	**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.
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 Minimization Measures

Not applicable.

V.2.1. Removal of Additional Risk Minimization Activities

Not applicable.

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serious infections (including mycobacterial and salmonella infections)	**Routine risk minimization measures:** • SmPC sections 4.3 (Contraindications), 4.4 (Special Warnings and Precautions for Use), 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction), 4.6 (Fertility, Pregnancy and Lactation), and 4.8 (Undesirable Effects) • PL sections 2 and 4 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQ for Serious Infections and Opportunistic Infections TOI TFUQ for TB **Additional pharmacovigilance activities:** STELARA UC/CD PASS using Swedish Registers • Final study report due date: 31 December 2028 STELARA UC PASS using SNDS • Final study report due date: 31 December 2027
Malignancy	**Routine risk minimization measures:** • SmPC sections 4.4 (Special Warnings and Precautions for Use) and 4.8 (Undesirable Effects) • PL section 2 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQ for Malignancies (including Lymphoma, Second and Secondary Malignancies) **Additional pharmacovigilance activities:** STELARA UC/CD PASS using Swedish Registers • Final study report due date: 31 December 2028 STELARA UC PASS using SNDS • Final study report due date: 31 December 2027
Cardiovascular events	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQ for CV Events **Additional pharmacovigilance activities:** STELARA UC/CD PASS using Swedish

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		Registers (MACE only) • Final study report due date: 31 December 2028 STELARA UC PASS using SNDS (MACE only) • Final study report due date: 31 December 2027
Serious depression including suicidality	**Routine risk minimization measures:** • SmPC section 4.8 (Undesirable Effects) • PL section 4 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Venous thromboembolism	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOIQ for VTE **Additional pharmacovigilance activities:** STELARA UC/CD PASS using Swedish Registers • Final study report due date: 31 December 2028 STELARA UC PASS using SNDS • Final study report due date: 31 December 2027
Long-term safety in pediatric psoriasis patients 6 years and older	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** CNTO1275PSO4056 (Pediatric Psoriasis Registry) • Final study report due date: 31 March 2033

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** CNTO1275PSO4056 (Pediatric Psoriasis Registry) • Final study report due date: 31 March 2033
Long-term safety in adult patients with moderately to severely active Crohn's disease	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** STELARA UC/CD PASS using Swedish Registers • Final study report due date: 31 December 2028
Long-term safety in adult patients with moderately to severely active ulcerative colitis	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** STELARA UC/CD PASS using Swedish Registers • Final study report due date: 31 December 2028 STELARA UC PASS using SNDS • Final study report due date: 31 December 2027

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** CNTO1275ISD3001 (UNITED) LTE • Final study report due date: 31 January 2030

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for STELARA (ustekinumab)

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

STELARA's Summary of Product Characteristics (SmPC) and Package Leaflet (PL) give essential information to healthcare professionals and patients on how STELARA should be used.

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

I. The Medicine and What it is Used For

STELARA is authorized for plaque psoriasis, psoriatic arthritis (PsA), pediatric plaque psoriasis, adult Crohn's disease (CD), ulcerative colitis (UC), and pediatric CD (see SmPC for the full indications). 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 STELARA's benefits can be found in STELARA's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/stelara

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

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

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

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

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, 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 STELARA is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of STELARA are risks that need special risk management activities to further investigate or minimize 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 STELARA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
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 adult patients with moderately to severely active ulcerative colitis 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 interleukin (IL)-12/23 may predispose patients to serious infections. 'Serious infections (including mycobacterial and salmonella infections)' is considered an important potential risk with STELARA based upon the theoretical risk identified from nonclinical data and in humans who are genetically deficient for the cytokines that are inhibited by STELARA (IL-12/23p40 or IL-12Rβ1). However, the risk of developing serious infections (including mycobacterial and salmonella infections) in subjects on anti-IL-12/23p40 therapy such as STELARA is currently unknown. Across clinical trials in all indications for which STELARA is approved, analysis for serious infections in pooled data during the controlled period does not suggest an increased risk of serious infection in the overall ustekinumab-treated population.
Risk factors and risk groups	*Serious infections* Risk factors for the development of serious infections include diabetes and other comorbidities, as well as the concomitant use of steroids, anti-tumor necrosis factor (TNF)s, other immunosuppressants, or other biologics. *Tuberculosis (TB)* The most common risk factors for the development of TB include conditions impairing the development of effective cell-mediated immunity to the infection (ie, advanced age, human immunodeficiency virus [HIV] infection), alcohol abuse, malignancy, corticosteroids or other immunosuppression, connective tissue disease, renal failure, diabetes, and pregnancy. A risk factor for the development of TB is exposure to TB, and patients who were born or lived in countries considered by the World Health Organization to have a high TB burden (incidence: >300 TB cases/100,000 population/year) or have travelled to these locations may be at higher risk. Exposure in the health care setting or in high-density institutions (ie, prisons) may also put patients at higher risk of development of TB. The possibility of latent TB must be considered, especially in patients who have immigrated from or travelled to countries with a high prevalence of TB or had close contact with a person with active TB. In patients who are severely ill or immunocompromised, tuberculin tests may yield false negative results. *Non-TB mycobacterial (NTM) infections* A retrospective/prospective review performed in Australia, found that significant risks for non-HIV-associated pulmonary *Mycobacterium avium*/*Mycobacterium intracellulare* complex (MAC) disease included male sex (odds ratios [OR]=2.1; 95% confidence interval [CI] 1.0 to 4.5) and age >50 years (OR=26.5; 95% CI 10.9 to 67.3). Similarly, in a United States (US) study including 933 patients with 1 or more NTM isolates, pulmonary disease prevalence was highest in persons aged >50 years (15.5 cases per 100,000 persons). In addition, chronic respiratory disease, especially chronic obstructive pulmonary disease treated with inhaled corticosteroid therapy is a strong risk factor for NTM pulmonary disease.

Important Potential Risk: Serious infections (including mycobacterial and salmonella infections)	
	Prolonged occupational exposure to soil was an important risk factor for MAC infection in a US study. *Salmonella* Factors that could increase risk of salmonella infection include activities that result in close contact with salmonella (eg, international travel, owning a pet bird or reptile) and health issues that weaken resistance to infection (eg, stomach or bowel disorders leading to use of antacids; recent antibiotic use; inflammatory bowel disease [IBD]; or impaired immunity from acquired immune deficiency syndrome, sickle cell disease, malaria, anti-rejection drugs taken after organ transplants, and corticosteroids).
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.3 (Contraindications), 4.4 (Special Warnings and Precautions for Use), 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction), 4.6 (Fertility, Pregnancy and Lactation), and 4.8 (Undesirable Effects) PL sections 2 and 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: STELARA UC/CD postauthorization safety study (PASS) using Swedish Registers STELARA UC PASS using the French Nationwide Claims Database (SNDS) See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Malignancy	
Evidence for linking the risk to the medicine	There is a theoretical risk of malignancy associated with administration of STELARA based on scientific literature pertaining to inhibition of IL-12/23. In the pooled controlled portion of clinical trials across indications, the rate of malignancy other than non-melanoma skin cancer (NMSC) was low and was balanced between the ustekinumab and comparator groups. Because malignancies tend to take a long time to develop, long-term follow-up is most relevant. In psoriasis patients treated for up to 5 years of continuous STELARA therapy, the risk of malignancies other than NMSC was not increased compared with the general US population. There was no evidence of an increased risk of malignancy through approximately 5 years of follow-up in CD patients and approximately 4 years of follow-up in UC patients treated with STELARA. Long-term effects of STELARA on existing malignancies or in patients with a history of malignancy are not known. In light of the theoretic risk and the longer latency period for the development of malignancy, the topic warrants continued surveillance and malignancy is considered an important potential risk.
Risk factors and risk groups	Among psoriasis patients, increased risk of solid cancers appears to be related to alcohol drinking and cigarette smoking. In addition, exposure to psoralen and ultraviolet A and immunosuppressants, including cyclosporin and possibly methotrexate (MTX), has been associated with squamous cell carcinoma in psoriasis patients. 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 minimization measures	Routine risk minimization measures: SmPC sections 4.4 (Special Warnings and Precautions for Use) and 4.8 (Undesirable Effects) PL section 2 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: STELARA UC/CD PASS using Swedish Registers STELARA UC PASS using SNDS See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Cardiovascular events	
Evidence for linking the risk to the medicine	The risk of developing cardiovascular (CV) events in subjects on anti-IL-12/23p40 therapy such as STELARA is currently unknown. A numeric imbalance in rates of investigator-reported major adverse cardiovascular events (MACE) was observed between ustekinumab- and placebo-treated subjects in the controlled portions of Phase 2 and Phase 3 trials in psoriasis, resulting predominantly from an imbalance in event rates from a smaller Phase 2 trial. Additional analyses performed internally by the Marketing Authorization Holder show that the overall rates of myocardial infarction and stroke with up to 5 years of treatment with STELARA in psoriasis patients are comparable with expected rates in either the general population or in the psoriasis population, and comparable to rates in trials of other biologics. Through approximately 5 years of follow-up in CD clinical trials and approximately 4 years of follow-up in UC clinical trials, the incidence of serious MACE was low in ustekinumab-treated subjects and placebo-treated subjects, with no consistent evidence that ustekinumab increases cardiovascular risk. Across indications, analysis of MACE in controlled portions of the pooled clinical trial data does not currently suggest a significant increased risk of MACE in subjects treated with ustekinumab. In summary, the totality of the currently available data does not suggest that ustekinumab increases the risk of MACE; however, in light of the imbalance of CV events in the short-term placebo-controlled portions of the psoriasis clinical trials and the known increased risk of these events in the psoriasis and PsA populations, CV events are considered an important potential risk for ustekinumab.
Risk factors and risk groups	Risk factors for the development of CV disease are well known and include hypertension, hypercholesterolemia, diabetes, smoking, age, male sex, obesity, and family history. The PsA, psoriasis, and CD populations share certain risk factors, such as increased CV risk, increased body weight, and increased body mass index.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: STELARA UC/CD PASS using Swedish Registers (MACE only) STELARA UC PASS using SNDS (MACE only) See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Serious depression including suicidality	
Evidence for linking the risk to the medicine	Psoriasis patients can have an increased risk for depression and, in rare cases, suicide. Depression has been identified as an ADR for STELARA (SmPC section 4.8 [Undesirable Effects] and PL section 4) based on a safety signal identified in the placebo-controlled period from the Phase 2 and Phase 3 psoriasis clinical trials. The incidence of serious depression including suicidality across indications remains low. The available safety data from clinical studies and postmarketing experience have not identified a safety signal of suicidal ideation or suicidal attempt (including completed suicide). However, based on the severity of these events, serious depression including suicidality is considered an important potential risk for STELARA.
Risk factors and risk groups	Risk factors for depression include older age and associated neurological conditions; uncontrolled, poorly treated psoriasis; recent childbirth; stressful life events; a personal or family history of depression; and selected medical comorbid conditions including psoriatic conditions and IBD. Suicide rates are twice as high in families of suicide victims.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.8 (Undesirable Effects) PL section 4 Additional risk minimization measures: None

Important Potential Risk: Venous thromboembolism	
Evidence for linking the risk to the medicine	Patients with IBD can have an increased risk for blood clots in veins due to their underlying condition and other risk factors (dehydration, use of catheters, prolonged immobilization, hospitalization, surgical interventions, oral contraceptive use, etc). Venous thromboembolism (VTE) was originally identified as an important potential risk based on data collected through 44 weeks of treatment in the ustekinumab CD clinical trials. Through approximately 5 years of follow-up in CD clinical trials and approximately 4 years of follow-up in UC clinical trials, while there is a slight imbalance across treatment groups in the reporting of all vascular thrombotic events, the overall incidences per 100 subject-years (~0.1 [~1%]) observed among STELARA-treated subjects in both the CD and UC populations are within the range reported in the IBD literature. Overall, safety results from the CD clinical trials through Week 272, UC clinical trials through Week 220, and clinical trials conducted for other indications, as well as cumulative postmarketing data, do not indicate an increased rate with ustekinumab treatment.
Risk factors and risk groups	Patients suffering from IBD, namely CD and UC, are more prone to thromboembolic complications compared with the general population. A study of IBD patients conducted in the United Kingdom reported that there was increased risk of VTE during disease flares and chronic activity. In a Danish population study that included children and adults, the highest risk of VTE was in the 0 to 20 years age group with a hazard ratio of 6.6 (95% CI 3.3 to 13.2), compared with 1.6 (95% CI 1.5 to 1.8) for the ≥60 years age group. The risk has also been reported to be greater for males (incidence rate of 1.34/1000 person-years [PY]) than for females (incidence rate of 0.73/1000 PY). Smoking and the need for steroid treatment have also been shown to be risk factors for VTE with ORs of 3.46 (95% CI 1.14 to 10.5) and 2.97 (95% CI 0.99 to 8.92), respectively.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: STELARA UC/CD PASS using Swedish Registers STELARA UC PASS using SNDS See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Long-term safety in pediatric psoriasis patients 6 years and older	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CNTO1275PSO4056 (Pediatric Psoriasis Registry) See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CNTO1275PSO4056 (Pediatric Psoriasis Registry) See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Long-term safety in adult patients with moderately to severely active Crohn's disease	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: STELARA UC/CD PASS using Swedish Registers See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Long-term safety in adult patients with moderately to severely active ulcerative colitis	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: STELARA UC/CD PASS using Swedish Registers STELARA UC PASS using SNDS See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CNTO1275ISD3001 (UNITED) LTE See section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization Development Plan

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

No studies are conditions of the marketing authorization or specific obligations of STELARA.

II.C.2. Other Studies in Postauthorization Development Plan

Study	Purpose of Study
CNTO1275PSO4056 (Pediatric Psoriasis Registry)	Objective: To confirm the long-term safety profile of STELARA use in pediatric patients 6 years and older and to explore any potential effect on growth and development in pediatric patients 6 years and older in-line with the consideration in the STELARA PIP. To address the safety concerns of: • 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.
PCSIMM002807 (STELARA UC/CD PASS using Swedish Registers)	Objective: To evaluate the long-term safety of STELARA in adult patients with moderately to severely active UC or CD. To address the safety concerns of: • Venous thromboembolism • Malignancy • Cardiovascular events (MACE only) • Serious infections (including mycobacterial and salmonella infections) • Long-term safety in adult patients with moderately to severely active ulcerative colitis • Long-term safety in adult patients with moderately to severely active Crohn's disease
PCSIMM002659 (STELARA UC PASS using SNDS)	Objective: To evaluate the long-term safety of STELARA in adult patients with moderately to severely active UC. To address the safety concerns of: • Venous thromboembolism • Malignancy • Cardiovascular events (MACE only) • Serious infections (including mycobacterial and salmonella infections) • Long-term safety in adult patients with moderately to severely active ulcerative colitis
CNTO1275ISD3001 (UNITED) LTE	Objective: To collect long-term safety data in pediatric patients 2 to <18 years of age who receive SC ustekinumab for at least 1 year after participating in a primary pediatric ustekinumab trial (CNTO1275CRD1001, CNTO1275PUC3001, CNTO1275CRD3004, and CNTO1275JPA3001). To address the safety concern of: • Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease

PART VII: ANNEXES

Table of Contents

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Table of Contents

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 Interest Questionnaire (TOIQ) for Venous Thromboembolism (VTE)

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

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

Manufacturer Control Number: Drug generic (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)

Manufacturer Control Number: Drug generic (TRADE) 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:

- ☐ Intradermal 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)		
PCR MTb			
Quantiferon TB Gold			

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

Manufacturer Control Number: Drug generic (TRADENAME):
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 tumor 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, clophosphamide, vincristine, doxorubicine, cyclosporine, biologics)

Medication	Indication	Dose/Route of Administration	Start Date/Stop Date (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)

MCN:

2. Diagnostics

Histopathologic diagnosis (Include the histopathology report):

Include malignancy stage, location of primary tumor, 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: Immunophenotype: 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*):

(Ref. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf)

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)	Results (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

Manufacturer Control Number: Drug generic (TRADE) 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-MMM-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
   ☐ Hyperlipidemia/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
   ☐ Hemorrhagic cerebrovascular accident
   ☐ Other (Specify):

   Relevant family history:
   ☐ Coronary disease ☐ Stroke
   ☐ Hyperlipidemia/Hypercholesterolemia/Hypertriglyceridemia
   ☐ Myocardial infarction
   ☐ Diabetes mellitus
   ☐ Family history of long QT syndrome
   ☐ Other (Specify):

MCN:

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)

Manufacturer Control Number: Date of Report: [dd-MMM-yyyy]
Product Generic (TRADE) 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

MCN:

☐ 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		

MCN:

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 (IgG and IgM) or beta-2 glycoproteins antibodies		
Antiphospholipid antibodies (IgG and IgM)		
Lupus anticoagulant		
Heparin antibodies		
ANA and ANCA		
IL6 levels		
ADAMTS13 Activity Assay		
Ceruloplasmin		
Direct Coombs test		
Complement C3, C4		
MethylenetetraHydrofolate 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 Additional Risk Minimization Activities

Not applicable.