European Union Risk Management Plan
STELARA® (ustekinumab)

Data lock point for current RMP	20 July 2020	Version number	21.1

QPPV Sign-off Date: 25 March 2021
RMP Version Number: 21.1
Supersedes Versions: 18.4 and 20.1
EDMS Number: EDMS-RIM-374539

QPPV Name(s):	Dr. Laurence OSTER-GOZET, PharmD, PhD
QPPV Signature:	The 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	21.1
Rationale for submitting an updated RMP	Consolidation of updates contained in the following HA-approved EU RMPs: • Version 18.4. EC decision: 09 March 2021. – Procedure EMEA/H/C/000958/II/0081/G. • Version 20.1. Positive opinion: 05 March 2021. – Procedure EMEA/H/C/000958/IB/0086.
Summary of significant changes in this RMP:	Consolidation of updates contained in the following HA-approved EU RMPs: • Version 18.4. – Addition of Week 96 data from Trial CNTO1275UCO3001 and Week 272 data from Trial CNTO1275CRD3003. • Version 20.1. – Change of milestone date for the submission of the final report for CNTO1275PSO4007 (Pregnancy Research Initiative).

Other RMP Versions Under Evaluation:

RMP Version Number	**Submitted on**	**Procedure Number**
Not applicable	Not applicable	Not applicable

Details of the Currently Approved RMP:

Version numbers of last agreed RMPs:	Version 18.4 Version 20.1
Approved within Procedures	EMEA/H/C/000958/II/0081/G (version 18.4) EMEA/H/C/000958/IB/0086 (version 20.1)
Dates of approval	09 March 2021 (version 18.4) (EC Decision) 05 March 2021 (version 20.1) (positive opinion)

TABLE OF CONTENTS

PART I: PRODUCT(S) OVERVIEW 6

PART II: SAFETY SPECIFICATION 9

MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S) .. 9

MODULE SII: NONCLINICAL PART OF THE SAFETY SPECIFICATION 26

MODULE SIII: CLINICAL TRIAL EXPOSURE 29
SIII.1. Brief Overview of Development 29
SIII.2. Clinical Trial Exposure 29

MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS 42
SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program 42
SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Program(s) .. 46
SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s) 46

MODULE SV: POSTAUTHORIZATION EXPERIENCE 48
SV.1. Postauthorization Exposure 48
SV.1.1. Method used to Calculate Exposure 48
SV.1.2. Exposure 49

MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION . 51

MODULE SVII: IDENTIFIED AND POTENTIAL RISKS 52
SVII.1. Identification of Safety Concerns in the Initial RMP Submission 52
SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP 52
SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP 52
SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP . 52
SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information 52
SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks 54
SVII.3.2. Presentation of the Missing Information 99

MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS 101

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES) 102
III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection 102
III.2. Additional Pharmacovigilance Activities 103
III.3. Summary Table of Additional Pharmacovigilance Activities 108

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES 113

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES) 114
V.1. Routine Risk Minimization Measures 114
V.2. Additional Risk Minimization Measures 120
V.2.1. Removal of Additional Risk Minimization Activities 120
V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities 120

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN 127
I. The Medicine and What it is Used For 127
II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks 127
II.A. List of Important Risks and Missing Information 128
II.B. Summary of Important Risks 129
II.C. Postauthorization Development Plan 143

II.C.1. Studies Which are Conditions of the Marketing Authorization 143
II.C.2. Other Studies in Postauthorization Development Plan 144

PART VII: ANNEXES 146
Annex 1: Eudravigilance Interface 147
Annex 2: Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program 148
Annex 3: Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan 153
Annex 4: Specific Adverse Drug Reaction Follow-up Forms 155
Annex 5: Protocols for Proposed and Ongoing Studies in RMP Part IV 186
Annex 6: Details of Proposed Additional Risk Minimization Activities 187
Annex 7: Other Supporting Data (Including Referenced Material) 188
Annex 8: Summary of Changes to the Risk Management Plan Over Time 206

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/SPC, Labelling and Package Leaflet
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 (PsA)</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>Crohn's disease</u> STELARA is indicated for the treatment of adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor (TNF)α antagonist or have medical contraindications to such therapies.

	Ulcerative colitis STELARA is indicated for the treatment of adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies.
	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. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment. *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. In these patients, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy. PsA 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. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment. Pediatric plaque psoriasis (6 years and older) The recommended dose of STELARA based on body weight is presented in the Summary of Product Characteristics (SmPC) section 4.2 (Posology and Method of Administration). STELARA should be administered at Weeks 0 and 4, then every 12 weeks thereafter. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment. 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.
	Proposed: Not applicable.

Pharmaceutical form(s) and strengths	Current: For SC use The solution is clear, colorless to light yellow. Solution for injection: 45 mg/0.5 mL and 90 mg/1 mL. Solution for injection in pre-filled syringe: 45 mg/0.5 mL and 90 mg/1 mL. For IV use The solution is clear, colorless to light yellow. 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.

A study reported an incidence of psoriasis of 230 per 100,000 person-years (PY) in 2005 in Italy (Vena et al 2010). 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 et al 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]: 75.0-82.9) in both sexes between 1970 and 2000 (Icen et al 2009)
- 82 per 100,000 PY (95% CI: 77-89) in women from 1991 to 2005 (Setty and Choi 2007).

Prevalence:

Psoriasis affects 1% to 3% of the population. According to the Global Burden of Disease study, there were approximately 65 million people with psoriasis in 2016 (GBD 2017). Approximately 15% to 20% of patients have extensive skin involvement or severe disease requiring systemic therapy (Abuabara et al 2010).

Using data from the CPRD, prevalence estimates in the UK were 2.8% between 1999 and 2013 (Springate et al 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 et al 2013). Other countries in northeast and southern Europe report higher values than the UK, ranging from 3.20% in Italy to 8.50% in Norway. In a large, multinational, population-based survey of psoriasis and PsA patients in North America and Europe, the prevalence of psoriasis and PsA ranged from 1.4% (Spain) to 3.3% (Canada; Lebwohl et al 2014). Of these, 79% of patients had psoriasis alone and 21% also had PsA.

Prevalence estimates of psoriasis in the US range from 2.2% to 3.15% (Parisi et al 2013). Findings from a nationally representative sample survey from the US that gathered data from 2009 to 2010 reported prevalence of psoriasis among adults aged 20 years and older as 3.2% (95% CI: 2.6%-3.7%). Consistent results reporting overall prevalence of psoriasis as 3.1% were published in another national US study (Helmick et al 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 et al 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 of psoriasis 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 et al 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 this decreased.

There are no established data about whether the prevalence of psoriasis differs between men and women. Parisi et al (2013) found that there were 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 a second study in Norway reported a slightly higher prevalence of psoriasis in women. Studies in Denmark, Australia, and China reported a higher prevalence of psoriasis in men.

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 et al 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 et al 2015).

Viral or bacterial infections are also a risk factor for psoriasis. For example, people with 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, obesity, and smoking tobacco (Psoriasis: Risk Factors, Mayo Clinic 2018).

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. Therapy used to treat psoriasis include (Psoriasis: Treatments and Drugs, Mayo Clinic 2018):

- Topical therapies (applied to the skin): This therapy includes 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 light)
- Systemic medications (oral or injected): This therapy is used for patients with moderate to severe psoriasis and includes retinoids, MTX, hydroxyurea, immunomodulator drugs (including apremilast, azathioprine [AZA], cyclosporine, and leflunomide), biologics (including adalimumab, etanercept, golimumab, guselkumab, infliximab, ixekizumab, and secukinumab), and thioguanine.

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

Since observational studies generally include a treated population, it is difficult to describe the course of the indication in the untreated population and to dissociate the effects of treatment from the natural history of the disease. This caveat 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% to 10% BSA) and severe (>10% BSA) psoriasis occurred in 35.8% and 12.4%, respectively, of patients (Yeung et al 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) rheumatologic disease (OR of 2.89 versus 2.01, respectively) compared with patients with mild disease (Yeung et al 2013).

Mortality

The risk of all-cause mortality for psoriasis patients is elevated compared with people without psoriasis (hazard ratio [HR]=1.21; 95% CI: 1.13-1.3) (Springate et al 2017). 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 et al 2015). In the UK, the overall mortality rate of psoriasis patients is 12.12 deaths per 1,000 PY. Mortality rates among patients with psoriasis were 22.19 per 1,000 PY for those receiving at least 1 DMARD (ie, with more severe disease) and 11.92 per 1,000 PY for those not prescribed DMARDs. Cardiovascular (CV) disease was the most commonly identified cause of death among both

psoriasis and unexposed patients, followed by infection and malignant neoplasms (Abuabara et al 2010).

Important Co-morbidities:

Co-morbidities that occur in adult patients with psoriasis include PsA; inflammatory bowel disease (IBD); non-melanoma skin cancer (NMSC), probably due to light therapy; psoriasis; depression; uveitis; obesity; metabolic syndrome (or components of it); CV disease; and type 2 diabetes (Pouplard et al 2013; Mayo Clinic 2018).

Indication: Pediatric psoriasis

Incidence:

A population-based study in the US over a 30-year period reported the overall age- and sex-adjusted annual incidence of pediatric psoriasis as 40.8 per 100,000 (95% CI: 36.6-45.1) from 1970 to 1999 (Tollefson et al 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: 29.3-37.0). Incidence of psoriasis in children increased significantly over time from 29.6 per 100,000 (1970 to 1974) to 62.7 per 100,000 (1995 to 1999; p<001) (Tollefson et al 2010).

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

Prevalence:

The estimated prevalence of pediatric psoriasis from population-based studies ranged from 0% to 2.1%. The highest values are from European studies, especially Italy (2.1%), Germany (1.3%), and the UK (1.3% for patients from 10 to 19 years of age) (Burden-Teh et al 2016). A claims-based study conducted in the US reported an annual prevalence of 128 cases per 100,000 individuals (95% CI: 124-131) in 2015 (Paller et al. 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 et al. 2018). 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 et al 2014). 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 et al 2013). Age- and sex-specific annual incidence of psoriasis in children reported in a population-based cohort in the US from 1970 to 1999 is shown below (Tollefson et al 2010). A rapid increase was observed in both sexes up to 7 years of age, with incidence remaining relatively flat thereafter.

	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

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 4-11 years old and 4.3% were 3 years old or younger in 2015 (Paller et al. 2018). In a large German health insurance study

of juvenile psoriasis, the prevalence of psoriasis showed an increasing trend with increasing age in 2005 is shown below (Augustin et al 2010).

Age (years)	Prevalence	Age (years)	Prevalence	Age (years)	Prevalence
<1	0.12%	7	0.56%	14	1.04%
1	0.22%	8	0.55%	15	1.22%
2	0.24%	9	0.56%	16	1.12%
3	0.20%	10	0.79%	17	1.17%
4	0.30%	11	0.72%	18	1.24%
5	0.40%	12	0.83%		
6	0.41%	13	1.00%		

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 et al 2011). Other identified risk factors include infection, stress (usually emotional or psychological) and a history of trauma (Burden-Teh et al 2016); this publication also cited obesity as a risk factor in agreement with data published by Ozden et al in 2014.

The Main Existing Treatment Options:

A recent review summarized the treatments used in the pediatric population for psoriasis (Tollefson 2014). Topical skin-directed treatment is sufficient treatment for most children, especially 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 for treatment of childhood psoriasis. Other topical treatments include vitamin D analogues (calcipotriene, 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 disease or refractory disease may require phototherapy and/or systemic treatment with medications such as MTX, cyclosporin, oral retinoids, and other biologic medications.

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 and psoriasis lesions tend to develop more often on the face and flexural areas in children.

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 et al 2015).

Patients with childhood-onset psoriasis are more likely to have significant disease and flares compared with those with adult-onset psoriasis (Burden-Teh et al 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 of it); obesity; diabetes mellitus; and CD (Augustin et al 2010).

Indication: Psoriatic arthritis

Incidence:

A recent meta-analysis of 28 population studies reported a pooled incidence of PsA of 8.3 per 100,000 PY (95% CI: 4.1-16.7). Interstudy heterogeneity was high, with incidence ranging from 3.0 to 41.3 cases per 100,000 PY (Scotti et al 2018). A large observational study conducted in the UK, Italy, France, Spain, and Germany in 2006 included 1,560 patients with psoriasis, of which 126 had PsA. An incidence of PsA among psoriasis patients (74 per 1,000 PY) was observed (Christophers et al 2010). In an Italian primary health care database study, PsA was present in 8% of 5,792 individuals with psoriasis diagnosed from 2001 to 2005 (Vena et al 2010). In Denmark, the incidence for PsA for 2011 was reported at 19.8 per 100,000 (Egeberg 2017b).

Prevalence:

The study by Scotti et al (2018) mentioned above reported a pooled prevalence of PsA of 133 per 100,000 population, ranging from 20 to 670 cases per 100,000 population. Interstudy heterogeneity was high, with some of the differences being explained by PsA detection criteria. In the study by Christophers et al (2010) mentioned above, PsA prevalence increased with time since psoriasis diagnosis, reaching 20.5% after 30 years. In a recent large, multinational, population-based survey of psoriasis and/or PsA patients conducted in 2005 in North America and Europe, the prevalence of psoriasis/PsA ranged from 1.4% to 3.3% (Lebwohl et al 2014). In this study, 79% of patients had psoriasis alone and 21% also had PsA. Other studies reported that 11% and 42% of patients with plaque psoriasis also experience PsA (Gelfand et al 2005; Gladman et al 2005). Another study used The Health Information Network (THIN), a large UK-based medical record database, to conduct a cross-sectional study. 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, giving an overall prevalence of 0.19% (95% CI: 0.185-0.193) (Ogdie et al 2013).

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

	Men		Women		All	
Age (years)	**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**

Risk Factors

Having psoriasis is the single greatest risk factor for developing PsA (Mayo Clinic: Psoriatic Arthritis 2014), with particular significance for lesions on nails. An infectious agent may also trigger the psoriatic process and 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 et al 2009).

Studies have suggested that there is a high risk for PsA among first-degree relatives (Mayo Clinic: Psoriatic Arthritis Risk Factors). 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 et al 2009).

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 DMARDs such as MTX, sulfasalazine, and leflunomide are used when poor prognostic indicators are present. Finally, TNFα inhibitor therapy is considered when inflammation persists despite traditional treatment. Intra-articular and entheseal injections can also be employed (Day et al 2012).

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) is reported in 40% of PsA patients and 87% have psoriatic lesions of the nail (Gladman et al 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 2009). In patients who have been followed for more than 10 years, 55% had 5 or more deformed joints (Gladman et al 2005).

Mortality

In a study that identified 8,706 patients from THIN, the mortality rate of PsA patients overall 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 in this study after adjusting for age and sex (Ogdie et al 2014; Ogdie et al 2017). Patients who were entered into the PsA database at the Royal National Hospital for Rheumatic Diseases between 1985 and 2007 were included in another study to examine mortality of PsA patients. Of 453 PsA patients (232 men, 221 women), a total of 27 died (16 men, 21 women). The overall standardized mortality ratio (SMR) for the PsA cohort was 0.82 with a wide CI that overlapped 1, suggesting that mortality in the PsA cohort did not differ significantly from the general UK population (Buckley et al 2010). The leading causes of death in this cohort were CV disease (38%), diseases of the respiratory system (27%), and malignancy (14%). 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 et al 2009).

Important Co-morbidities:

Co-morbidities that occur in PsA patients include diabetes mellitus; obesity; metabolic syndrome (or components of it); CV disease; IBD; uveitis; and depression (Haddad and Zisman 2017).

Indication: Crohn's disease

Incidence:

In a systematic review of worldwide incidence of CD from 1990 to 2016, 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 et al, 2018).

For specific regions of Europe, 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 et al, 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 et al 2012). Another study reported that the incidence of CD in Europe ranges from 0 to 11.5 per 100,000 PY (Burisch and Munkholm 2015). A study in Finland between 2000 and 2007 revealed an overall incidence of 9.2 per 100,000 population (Hovde and Moum 2012; Jussila et al 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 to 1990) to a peak at 7.1 per 100,000 population (1997 to 1999) before stabilizing at 6.7 per 100,000 population from 2006 to 2007 (Chouraki et al 2011). A study conducted in Denmark estimated an incidence of CD from 1980 to 2013 as 9.1 (95% CI: 8.7-9.5) per 100,000 population (Lophaven et al 2017). In the Netherlands, the incidence of CD was reported as 10.5 per 100,000 PY (de Groof et al 2016).

Generally, the incidence of CD is increasing in the Western world, including North America, Europe, Australia, and New Zealand (Aniwan et al 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 et al, 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 et al, 2018). Another study reported prevalence in Europe ranging from 1.5 to 213 per 100,000 persons (Burisch and Munkholm 2015). In the Netherlands, the prevalence of CD has been reported as 171.8 per 100,000 population from 2004 to 2010 (de Groof et al 2016). More recently, a Spanish study reported a prevalence of 191.4 per 100,000 population in 2016 (Brunet et al, 2018).

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 to 35 years of age), followed by a small peak in older patients (Sonnenberg 2010). The median age of onset is 30 years (Feuerstein and Cheifetz 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 women than men during childhood, but then increased in women compared to men in the 10 to 14 year age group, and then remains higher in women than men, except for the 30 to 34 year age group (Shah et al, 2018). For example, 1 study in the UK from 1986 to 2003 found 62% of CD patients were female and another study in Denmark showed 54% of CD patients were female (Hovde and Moum 2012). The aforementioned study by Chouraki et al (2011) in France also showed a predominance of women 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 men and women (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 and Moum 2012).

Occurrence of CD seems to vary according to geographical location. Crohn's disease is more common in the industrialized world compared with non-industrialized countries (Feuerstein and Cheifetz 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 and Moum 2012). Another review suggested a northwest/southeast gradient in IBD incidence (Burisch et al 2013).

Risk Factors

Risk factors for CD include being younger than 30 years of age, being of Ashkenazi Jewish descent or Caucasian, having a close relative with the disease, and living in an urban area or in industrialized areas. A low-fiber and high-fat diet and certain medications (such as antibiotics, NSAIDs, and oral contraceptives) are also identified as risk factors for CD (Aniwan et al 2017), as well as having had an appendectomy or tonsillectomy (Piovani 2019). The most important controllable risk factor is cigarette smoking (Crohn's Disease: Risk Factors, Mayo Clinic, 2011).

<u>The Main Existing Treatment Options</u>:

The goal of medical treatment of CD is to reduce inflammation that triggers signs and symptoms of the condition 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 relieve signs and symptoms, of the disease. Examples include antidiarrheals, laxatives, pain relievers, iron supplements, vitamin B-12 shots, 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 (Crohn's disease: Treatments and drugs, Mayo Clinic 2018). For example, rates of bowel resection procedures range from 12% within 1 year of diagnosis in Denmark to 35% within 5 years in the UK (Hovde and Moum 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 and Moum 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 et al 2013). Similarly, 27.1% of CD patients in Europe develop stricturing disease and 29.4% develop penetrating disease within 10 years of diagnosis (Burisch et al 2013).

Mortality

A meta-analysis reported an increased mortality ratio in patients with CD (SMR=1.39, 95% CI: 1.30-1.50; Burish 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 et al 2013). A Spanish study reported a mortality rate of 17.0 per 100,000 population in 2016 (Brunet et al, 2018).

In a study from Ireland including 1,101 patients with CD <65 years of age, a total of 29 of these patients died before the age of 65 years during a mean follow-up of 8.9 years (O'Toole et al 2014). Data based on a prospective study including 5,315 patients with CD (diagnosed either from 1987 to 1993 and from 2000 to 2007 and followed through the end of 2010) reported a 33% increased overall mortality in these patients (SMR=1.33; 95% CI: 1.21-1.46; Jussila et al 2014). Data based on a prospective IBD register in Finland were collected for CD patients from 1986 to 2007. The authors found an SMR of 1.14 (Manninen et al 2012). For cause-specific mortality, the risk of death in diseases of the digestive system was significantly increased in

CD (SMR=5.83) and mortality in colorectal cancer was non-significantly increased (SMR=1.88).

Conversely, another report found no difference between CD patients and controls in overall mortality (HR=1.35, 95% CI: 0.94-1.94, p=0.10). A study in southeastern Norway followed all patients diagnosed with CD between 1990 and 1993 for 20 years (Hovde et al 2013). 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.

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 disorders (Román and Muñoz 2011; Burisch et al 2013; Cury et al 2013; Crohn's and Colitis Foundation 2012; Bernstein 2019).

Indication: Ulcerative colitis (UC)

Incidence:

In a systematic review of 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 et al, 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 et al, 2018). A national study conducted in Denmark, which included all ages, estimated the incidence of UC in 2013 to be 18.6 (95% CI: 18.0-19.2) per 100,000 population (Lophaven et al 2017). In the Netherlands, the incidence has been reported at 17.2 per 100,000 PY (de Groof et al 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: 16.1-23.9) per 100,000 population (Sjöberg et al 2013). Another regional Swedish study reported an incidence of 18.1 per 100,000 population in 2010 (Eriksson et al 2017).

Prevalence:

In a systematic review of 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 et al, 2018).

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 et al, 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 et al 2016). The study by Molodecky et al (2012) mentioned previously presented 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). The study by Eriksson et al (2017) reported the point prevalence for 2010 to be 474 (95% CI: 444-506) per 100,000 population in Sweden. More recently, a Spanish study reported a prevalence of 353.9 per 100,000 population in 2016 (Brunet et al, 2018).

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 with another peak between the ages of 50 and 80 years (Gajendran et al, 2019). A regional study conducted in Spain reported the incidence rate for UC in women was 2.7 per 100,000 population and 5.1 per 100,000 population in men for 2007 to 2008 (Cueto

Torreblanca et al 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 et al, 2018).

Risk Factors

Risk factors for UC include age (disease onset is usually <30 years), being white or of Ashkenazi Jewish descent, or having a family history of the disease (Mayo Clinic: Ulcerative Colitis Risk Factors 2018). A high-fat diet may also slightly increase the chance of developing UC (NIDDK 2017). There is also evidence that use of NSAIDs, oral contraceptives, and antibiotics may be associated with an increased risk of UC (Ye et al 2015).

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 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: Ulcerative Colitis, 2018).

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: Ulcerative Colitis Diagnosis and Treatment, 2018).

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 the patients (Cosnes et al 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% patients require UC-related hospitalization (Fumery et al, 2018). In general, over a 10-year period, 50% to 55% remit, approximately 37% of patients 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 et al, 2018). Approximately 20% to 30% of patients require a colectomy after 25 years of disease activity (Gajendran et al, 2019).

Mortality

A prospective IBD register in the catchment area of Finland which followed a set of UC patients from 1986 to 2007 reported a SMR of 0.90 (95% CI: 0.77-1.06) (Manninen et al 2012). A Spanish study reported a mortality rate of 19.4 per 100,000 population in 2016 (Brunet et al, 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 and Muñoz 2011; Burisch et al 2013).

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 from Nonclinical Studies

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.	Based on animal studies, there is a large safety margin for humans administered ustekinumab IV and SC (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 et al 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 et al 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.
Other	
Hepatotoxicity and nephrotoxicity	
No evidence of hepatotoxicity or nephrotoxicity was observed in toxicity studies based on clinical pathology and histopathology evaluations.	Based on animal studies, there is a large safety margin for humans administered ustekinumab IV and SC (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. Infection 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 et al 2006; Torti and Feldman 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.

Summary of Nonclinical Safety Concerns

Important identified risks	None
Important potential risks	Serious infections (including mycobacterial and salmonella infections)
	Malignancy
Missing information	None

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 patients ≥6 years of age with moderate to severe plaque psoriasis, the treatment of adult patients with active PsA, the treatment of adult patients with moderate to severe CD, and the treatment of adult patients with moderately to severely active UC.

The use of ustekinumab in systemic lupus erythematosus is currently being studied. The indications of atopic dermatitis, rheumatoid arthritis, multiple sclerosis, sarcoidosis, primary biliary cirrhosis, and axial spondyloarthritis have been investigated, but are no longer being pursued due to lack of efficacy.

SIII.2. Clinical Trial Exposure

Table SIII.1 through Table SIII.8 present available integrated exposure data across indications based on the data lock point of 11 November 2019 for adult trials and 27 November 2018 for 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. In addition, the visit window of ±1 to 2 weeks was also taken into consideration.

The psoriasis Phase 2 trial (C0379T04) had a 20-week placebo-controlled period, but subjects were considered to have 6 months of exposure in the controlled period if the duration between the first and last ustekinumab administration was at least 14 weeks since exposure would continue for 6 months. The following convention was used to calculate exposure:

- Subjects in whom the duration between the first and last ustekinumab administration 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 administration 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 administration were counted as having at least 18 months of exposure
- Subjects with at least 88 weeks between the first and last ustekinumab administration were counted as having at least 2 years exposure
- Subjects with at least 140 weeks between the first and last ustekinumab administration were counted as having at least 3 years of exposure
- Subjects with at least 192 weeks between the first and last ustekinumab administration were counted as having at least 4 years exposure
- Subjects with at least 240 weeks between the first and last ustekinumab administration were considered to have at least 5 years exposure.

Exposure During Controlled Portions of Clinical Trials

Table SIII.1 through Table 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 in the integrated tables as this dataset was in Japanese and not available for pooling; therefore, the exposure data for this Japanese trial are presented separately.
- 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 which is approximately 6.0 mg/kg. 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

Table SIII.5 through Table 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 also applies here.
- Pediatric psoriasis: CNTO1275PSO3006 and CNTO1275PSO3013 (through to Week 56)
- PsA: C0743T10, CNTO1275PSA3001, and CNTO1275PSA3002
- CD: C0379T07, C0743T26, CNTO1275CRD3001, CNTO1275CRD3002 and CNTO1275CRD3003 (Week 272 database lock)
- UC: CNTO1275UCO3001 induction and CNTO1275UCO3001 maintenance (Week 96 database lock)

The caveats regarding weight-range-based doses for CD and UC trials discussed above also apply for Table SIII.7. Also note that, as outlined above, in pediatric psoriasis trial CNTO1275PSO3006, 2 distinct, weight-based ustekinumab dosages were studied (the standard dosage and the half-standard dosage). In pediatric psoriasis trial CNTO1275PSO3013, all subjects received the standard weight-based dosage (0.75 mg/kg for subjects weighing <60 kg, 45 mg for subjects weighing ≥60 kg to ≤100 kg, and 90 mg for subjects weighing >100 kg).

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	157
Duration of ustekinumab exposure		
≥ 6 months[b]	152	157
≥ 1 year[c]	106	119
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
Ulcerative colitis study[a]		
Subjects treated with ustekinumab	826	1256
Duration of ustekinumab exposure		
≥ 6 months[b]	544	1012
≥ 1 year[c]	497	976
≥ 2 years[d]	430	880
All studies[a]		
Subjects treated with ustekinumab	7561	15396
Duration of ustekinumab exposure		
≥ 6 months[b]	5004	13878
≥ 1 year[c]	3889	12980
≥ 2 years[d]	2868	11565
≥ 3 years[e]	1990	9690
≥ 4 years[f]	1845	9180
≥ 5 years[g]	1148	5861

[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). Pediatric psoriasis studies include CNTO1275PSO3006 and CNTO1275PSO3013. Ulcerative Colitis study includes CNTO1275UCO3001 (Induction Study and Maintenance Study through Week 96 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 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	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	17	27	28
≥ 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
Ulcerative colitis study[a]				
Age (yrs)				
< 45	275	421	201	301
≥ 45 to < 65	198	299	109	171
≥ 65	27	40	16	24
All studies[a]				
Age (yrs)				
≥ 6 to < 12	17	17	27	28
≥ 12 to ≤ 15	26	25	29	32
> 15 to < 18	28	29	27	26
≥ 18 to < 45	2349	4775	1573	2915
≥ 45 to < 65	1902	4308	1199	2500
≥ 65	218	419	166	322

[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). Pediatric psoriasis studies include CNTO1275PSO3006 and CNTO1275PSO3013. Ulcerative Colitis study includes CNTO1275UCO3001 (Induction Study and Maintenance Study through Week 96 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	101
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
Ulcerative colitis study[a]		
6.0 mg/kg[e]	504	254
90 mg[e]	581	862
130 mg[e]	321	139
All studies[a]		
Standard dosage	98	101
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]	133	51
4.5 mg/kg	64	28
6.0 mg/kg[de]	1105	463
45 mg[bc]	2409	4891
63 mg	116	64
90 mg[bcde]	4227	9284
130 mg[e]	1075	356
270 mg[d]	85	40

[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). Pediatric psoriasis studies include CNTO1275PSO3006 and CNTO1275PSO3013. Ulcerative Colitis study includes CNTO1275UCO3001 (Induction Study and Maintenance Study through Week 96 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 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[ab]		
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	143
Black or African American	0	0
Asian	7	7
American Indian or Alaskan native	3	3
Native Hawaiian or other Pacific Islander	0	0
Other	4	2
Unknown	1	0
Not reported	1	1
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
Ulcerative colitis study[a]		
Race		
White	623	947
Black or African American	8	11
Asian	127	198
American Indian or Alaskan native	0	0
Native Hawaiian or other Pacific Islander	0	0
Other	27	39
Unknown	3	2
Not reported	38	57

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
All studies[ab]		
Race		
White	6236	13467
Black or African American	140	284
Asian	787	1023
American Indian or Alaskan native	4	4
Native Hawaiian or other Pacific Islander	2	3
Other	173	316
Unknown	8	10
Not reported	56	89

[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). Pediatric psoriasis studies include CNTO1275PSO3006 and CNTO1275PSO3013. Ulcerative Colitis study includes CNTO1275UCO3001 (Induction Study and Maintenance Study through Week 96 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 Studies 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.
Considered to be included as missing information (Yes/No)	No.
Rationale (if not included as missing information)	Serious systemic hypersensitivity reaction is an important identified risk for STELARA. 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, 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.**
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.
Considered to be included as missing information (Yes/No)	No

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
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, the SmPC notes that 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.
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 is unknown whether ustekinumab is excreted in human milk.
Considered to be included as missing information (Yes/No)	No.
Rationale (if not included as missing information)	Exposure during pregnancy is an important potential risk for STELARA. Summary of Product Characteristics section 4.6 (Fertility, Pregnancy and Lactation) notes lack of adequate data regarding the use of ustekinumab in pregnant women, advises against use during pregnancy, and advises for the use of effective methods of contraception during treatment and up to 15 weeks after treatment.
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.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Considered to be included as missing information (Yes/No)	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. Summary of Product Characteristics section 4.4 (Special Warnings and Precautions for Use) notes that caution should be exercised when considering concomitant use of other immunosuppressants or when transitioning from other immunosuppressive biologics.
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. Other immunosuppressive biologics have been associated with lymphoma. Therefore, patients with lymphoma were excluded.
Considered to be included as missing information (Yes/No)	Yes.
Rationale (if not included as missing information)	Not applicable.
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.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Considered to be included as missing information (Yes/No)	No
Rationale (if not included as missing information)	Clinical experience suggests the immunosuppression seen with ustekinumab is minimal, however the SmPC recommends that before live viral or live bacterial vaccination, treatment with STELARA should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination (SmPC section 4.4 [Special Warnings and Precautions for Use]).
Criterion 10:	**Received allergy immunotherapy for prevention of anaphylactic reactions.**
Reason for being an exclusion criterion	At the time the Phase 3 clinical trials protocols were written, there was concern about a theoretical risk of decreased efficacy of allergy immunotherapy associated with IL-12/IL-23 blockade.
Considered to be included as missing information (Yes/No)	No
Rationale (if not included as missing information)	Routine pharmacovigilance monitoring 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 future pharmacovigilance activities will 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.
Considered to be included as missing information (Yes/No)	No
Rationale (if not included as missing information)	The impracticalities 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	The global safety database was searched for all reports of pregnancy exposure across all ustekinumab clinical trials cumulatively through 31 December 2019. A total of 92 pregnancies through maternal exposure and 79 pregnancies through paternal exposure were reported from clinical trials.
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. As presented in Table SIII.8, the majority of subjects in the STELARA clinical trials were white.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other: pediatric patients	The safety of STELARA in pediatric patients has been or is currently being studied in several pediatric trials. Exposure by age group is presented by indication in the All Clinical Trials Population in Table SIII.6. The exposure in the indication of pediatric psoriasis (≥6 to <18 years of age) was 71 male subjects and 83 female subjects. Clinical trials are also ongoing in pediatric CD (2 to <18 years of age) and pediatric psoriasis (≥6 to <12 years of age; CNTO1275PSO3013 main study [through Week 56] completed, long-term extension ongoing).

Summary of Missing Information Due to Limitations of the Clinical Trial Program

Use in patients with a history of latent tuberculosis or tuberculosis
Use in patients with concurrent malignancy or a history of malignancy
Use in patients with recent or concomitant use of immunosuppressive therapy other than methotrexate, 6-mercaptopurine, azathioprine, 5-aminosalicylic acid, and corticosteroids
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

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

SV.1.1. Method used to Calculate Exposure

Reporting frequencies calculated using exposure data do not reflect occurrence rates. Multiple factors influence the reporting of spontaneous events and therefore, caution must be exercised in the analysis and evaluation of spontaneous reports. In addition, product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the time a medication is distributed until it is used by a patient.

Worldwide patient exposure (person-times estimates):

Patient exposure was estimated by calculation from company distribution data of STELARA. In addition, estimates were made as to how much medication on average equals 1 PY of exposure. The recommended dose for STELARA varies by country and region. The exposure in subject-years is calculated using posology in approved prescribing information, regional estimates based on usage of the low versus high dose and patient compliance with these dosing regimens. Note that these estimates use the most recent information available. Cumulative exposure estimates could be different from previous reports due to refining of the exposure algorithm with updated data over time.

Additional stratifications for ustekinumab exposure:

Stratification information in the commercial setting for this drug is very limited. Information is provided using IQVIA (formerly IMS Health) (Vendor) data where possible and appropriate. Market research sources for non-study exposure data are unavailable for breakdowns such as: usage in pregnant or breastfeeding women, usage in hepatic impairment population, and usage in renal impairment population.

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

Prescription sales stratified by age and sex available from IQVIA (formerly IMS Health) (MIDAS™) for the EU and are presented as a percentage of total percentage of prescription sales.

Further stratification such as sex within age group are not provided since it is not appropriate to stratify to this level of detail based on information available from IQVIA (formerly IMS Health) for these subcategories. Prescription units are reported in 1000s and, in some cases, less than 1000 prescriptions were recorded.

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 ustekinumab.

SV.1.2. Exposure

Worldwide Patient Exposure (Person-time Estimates)

Cumulative Exposure to Ustekinumab (Launch to 31 December 2019)

Region	Total mg	Person-Years
European Union	124,017,019	574,221
United States	166,166,231	731,911
Canada	34,011,536	151,019
Rest of World	40,990,770	210,761
Total[a]	**365,185,556**	**1,667,912**

[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.

The estimated cumulative worldwide exposure to ustekinumab from launch to 31 December 2019 is 1,667,912 person-years.

EU Exposure by Age and Sex Presented as a Percentage of Prescription Sales

Postmarketing (Nonstudy) Ustekinumab Exposure by Age Group in Europe (01 October 2016 to 30 September 2019)

Age Groups (Years)[a]	EU[b] (265,698 Rx[c])
0 to 17	0.12%
18 to 35	19.25%
36 to 64	71.30%
>65	9.33%

Note: Data could not be further stratified into age groups of 6 to 12 and 13 to 17 years as the data are received in a standard format from IQVIA.

Key: EU=European Union; Rx=Prescriptions.

[a] Regional Rx data by age are only available for the last 3 years ending September 2019.

[b] Data stratified by age are only available in the EU for the following G5 countries: France, Germany, and Spain.

[c] Includes retail channels.

Postmarketing (Nonstudy) Ustekinumab Exposure by Age Group Outside Europe (01 October 2016 to 30 September 2019)

Age Groups (Years)[a]	Non-EU[b] (1,308,792 Rx[c])
0 to 17	0.18%
18 to 35	21.40%
36 to 64	63.84%
>65	12.95%
Age Unspecified	1.63%

Note: Data could not be further stratified into age groups of 6 to 12 and 13 to 17 years as the data are received in a standard format from IQVIA.

Key: EU=European Union; Rx=Prescriptions.

[a] Regional Rx data by age are only available for the last 3 years ending September 2019.

[b] Data stratified by age are only available in the EU for the following G5 countries: Canada, Japan, and the United States.

[c] Includes retail channels.

Post-marketing (Nonstudy) Ustekinumab Exposure by Sex (01 October 2016 to 30 September 2019)

Country	Females[a]	Males[a]	Patient Sex Unidentified[a]
Canada (193,810 Rx[b])	54.65%	41.99%	3.36%
France (35,140 Rx[b])	33.28%	66.72%	0.00%
Germany (78,968 Rx[b])	42.43%	57.57%	0.00%
Japan (286,238 Rx[b])	20.57%	73.52%	5.91%
Spain (151,590 Rx[b])	39.32%	60.68%	0.00%
United States of America (828,744 Rx[b])	47.53%	52.47%	0.00%

Key: Rx=Prescriptions.

[a] Regional Rx data by sex are only available for the last 3 years ending September 2019. Data are only available for Canada, France, Germany, Japan, Spain, and the United States.

[b] 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 PK/pharmacodynamic characteristics 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

Not applicable.

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

Important identified risks associated with the use of STELARA:

- Serious systemic hypersensitivity reactions
- Facial palsy
- Pustular psoriasis
- Erythrodermic psoriasis.

Important potential risks that may be associated with the use of STELARA:

- Serious infections (including mycobacterial and salmonella infections)
- Malignancy
- Cardiovascular events
- Serious depression including suicidality
- Reversible posterior leukoencephalopathy syndrome
- Venous thromboembolism
- Exposure during pregnancy.

Missing information for STELARA:

- Use in patients with a history of latent tuberculosis or tuberculosis
- Use in patients with concurrent malignancy or a history of malignancy
- Use in patients with recent or concomitant use of immunosuppressive therapy other than methotrexate, 6-mercaptopurine, azathioprine, 5-aminosalicylic acid, and corticosteroids
- 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.

The methodology for identifying clinical events for the important identified and important potential risks was 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 (psoriasis, PsA, CD, and UC) 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 since 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 both the 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 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 since the average follow-up was generally longer for the ustekinumab-treated subjects than the subjects receiving control agents. Additionally, the seriousness/outcomes and severity were summarized for ustekinumab-treated subjects.

In the pediatric psoriasis clinical trials (CNTO1275PSO3006 and CNTO1275PSO3013), only events of 'Serious infections' and 'Exposure during pregnancy' were reported, as shown in Table SVII.7 and Table SVII.14, respectively.

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

Important identified risk – Serious systemic hypersensitivity reactions

Potential mechanisms:

Serious systemic hypersensitivity reactions can generally be characterized as anaphylactic/anaphylactoid type reactions or immune complex-mediated/serum sickness type reactions (Type I or Type III hypersensitivity reactions by Gell and Coombs criteria). The symptoms as well as timing of these reactions are different. Anaphylactic/anaphylactoid reactions generally occur shortly (minutes to hours) after antigen exposure, while serum sickness-type reactions are delayed occurring days after exposure.

Treatment with mAbs may be associated with the development of antibodies against the therapeutic agent. Subjects who have developed antibodies to therapeutic proteins may be more likely to experience hypersensitivity reactions. There was no apparent relationship between the development of antibodies to ustekinumab and the development of hypersensitivity reactions.

Evidence source(s) and strength of evidence:

Serious systemic hypersensitivity reactions have been noted in the clinical trial program. Serious systemic hypersensitivity reactions related to ustekinumab have been reported in the postmarketing setting. Serious hypersensitivity reactions are considered an ADR for STELARA (SmPC section 4.8 [Undesirable Effects] and Package Leaflet section 4).

Characterization of the risk – Data:

Table SVII.1: Important Identified Risk – Serious Systemic Hypersensitivity Reactions; 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	79.1	11.5	107.0
Frequency[b]										
Ustekinumab vs	0.0% vs	0.1% vs	0.0% vs	0.0% vs	0.0% vs	0.2% vs	0.0% vs	0.0% vs	0.0% vs	0.1% vs
Placebo/Comparator[c]	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.3%	<0.1%	<0.1%
Odds ratio (95% CI)	-	-	-	-	-	-	-	-	-	-
Seriousness/outcomes										
Was Serious	0 (0.0%)	1 (<0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (<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%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.2%)	0 (0.0%)	0 (0.0%)	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%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	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%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	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 96 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 Periodic Benefit Risk Evaluation Report (PBRER)/Periodic Safety Update Report (PSUR) and coded to relevant MedDRA Standardized MedDRA Query (SMQ[s]) and/or PT(s). Based on the review of the data to date, no new safety information was identified for the important identified risk of 'Serious systemic hypersensitivity reactions.'

The serious systemic hypersensitivity reactions reported in ustekinumab clinical trials were related to stimuli other than ustekinumab (food and gadolinium).

The impact of 'Serious systemic hypersensitivity reactions' on an individual patient can vary from serious to potentially fatal, depending on the severity of the event. An event such as anaphylaxis can be serious or fatal and require emergency medical treatment or hospitalization. Early recognition and diagnosis as well as withdrawal of the suspected drug and initiation of appropriate treatment are important to minimize the impact on the patient.

No fatalities have been reported due to serious systemic hypersensitivity reactions related to STELARA.

Risk factors and risk groups:

In clinical trials for STELARA, there was no apparent association between a subject's antibody-to-ustekinumab status and hypersensitivity reactions. There are no known risk factors for the development of serious systemic hypersensitivity with ustekinumab.

Preventability:

STELARA is contraindicated in patients with a known hypersensitivity to the active substance or to any of the excipients (SmPC section 4.3 [Contraindications]).

The predictability and preventability of serious systemic hypersensitivity reactions with administration of STELARA is not known.

Impact on the risk-benefit balance of the product:

Serious systemic hypersensitivity reactions to ustekinumab occur infrequently and do not have a significant negative impact on the risk-benefit balance of the product.

Further characterization of the incidence of systemic hypersensitivity reactions is conducted through routine pharmacovigilance activities and registries.

Public health impact:

Serious systemic hypersensitivity reactions to ustekinumab occur infrequently and are unlikely to have any significant public health impact.

Medical Dictionary for Regulatory Activities (MedDRA) term for Annex 1:

SMQ: Hypersensitivity (narrow).

Important identified risk – Facial palsy

Potential mechanisms:

The etiology of Bell's palsy (facial palsy) is unknown, although genetic, vascular, infectious, and immunological causes have been proposed. Increasing evidence suggests that the main cause of Bell's palsy is reactivation of herpes viruses (herpes simplex or herpes zoster) from the cranial nerve ganglia (Finsterer 2008; Holland and Weiner 2004). Additionally, epidemiological data suggests that facial palsy may be associated with moderate to severe psoriasis or the therapies used to treat it.

Currently, there is no known mechanism by which STELARA could induce facial palsy. It is plausible, that as a selective immunosuppressant, STELARA could increase the risk of primary or reactivated viral illnesses that may be associated with Bell's palsy.

Evidence source(s) and strength of evidence:

Facial palsy was reported in ustekinumab clinical trials across indications, as well as in the postmarketing setting as spontaneous reports in psoriasis patients. Due to the lack of data on facial palsy in psoriasis, the MAH performed an epidemiologic analysis and found that the incidence of facial palsy in ustekinumab clinical trials was similar to that in the general population in the US.

Facial palsy is included as an ADR for STELARA (SmPC section 4.8 [Undesirable Effects] and Package Leaflet section 4).

Characterization of the risk – Data:

Table SVII.2: Important Identified Risk - Facial Palsy; 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	79.1	11.5	107.0
Frequency[b]										
Ustekinumab vs	0.0% vs	0.2% vs	0.0% vs	0.0% vs	0.1% vs	0.1% vs	0.0% vs	0.0% vs	<0.1% vs	0.1% vs
Placebo/Comparator[c]	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Odds ratio (95% CI)	-	-	-	-	-	-	-	-	-	-
Seriousness/outcomes										
Was Serious	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%)
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%)	5 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (<0.1%)	6 (0.1%)
Did not recover (Persisted)	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	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%)
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%)	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%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (<0.1%)	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 96 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/PSUR 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 identified risk of 'Facial palsy.' As noted above, the incidence of facial palsy in ustekinumab clinical trials was consistent with that in the general population.

In most cases of Bell's palsy, only facial muscle weakness occurs. The facial paralysis is temporary, though cosmetically undesirable. In severe cases of Bell's palsy, the condition can be physically debilitating because the facial muscles on the affected side are completely paralyzed and the condition is associated with drooling, inability to close the eye, altered facial sensation, and taste anomalies.

There is no specific treatment available to hasten or lessen the palsy and the disability may require months to resolve. Most patients recover without treatment: 71% achieve complete recovery and 84% achieve near-normal function. However, facial weakness may be permanent in some patients. Recovery from Bell's palsy depends on the extent and severity of damage to the VIIth cranial nerve.

Risk factors and risk groups:

There is no race, geographic, or sex predilection for facial palsy. It can be seen in patients of any age but increases over the age of 65 years and decreases under the age of 13 years. The risk of Bell's palsy is 3 times greater during pregnancy, especially in the third trimester or in the first postpartum week (Hilsinger et al 1975). Diabetes, hypertension, and hyperlipidemia have all been associated with Bell's palsy in the literature (Paolino et al 1985; Pecket and Schattner 1982). A positive family history is elicited in 8% of patients (Peitersen 2002). In a Finnish study, the 2 most common causes of facial palsy in children were Borrelia burgdorferi (30%) and varicella zoster virus (11%) (Kanerva et al 2013). It is common for patients with facial palsy to have had a history of a recent viral illness.

Preventability:

The preventability of facial palsy is unknown.

No testing is available to identify at-risk patients.

Impact on the risk-benefit balance of the product:

Cases of facial palsy reported in association with ustekinumab use are infrequent and do not have a significant negative impact on the risk-benefit balance of the product.

Further characterization of the incidence of facial palsy and evaluation of risk factors associated with this condition are conducted through routine pharmacovigilance activities and registries.

Public health impact:

The potential public health impact is not known.

MedDRA term for Annex 1:

High level term (HLT): Facial cranial nerve disorders.

Important identified risk – Pustular psoriasis

Potential mechanisms

Paradoxic worsening and new-onset psoriasis have been described with TNFα inhibitors and other biologic treatments for psoriasis (eg, rituximab, efalizumab, and anakinra). One theory postulates disruption in cytokine balance induced by TNF blockade may allow for unopposed interferon-α production by plasmacytoid dendritic cells in genetically predisposed individuals. Plasmacytoid dendritic cells are found in the normal skin of psoriasis patients, in early psoriatic plaques, and in patients with other inflammatory autoimmune disease. Another theory suggests that alternative key cytokines (eg, IL-17, IL-22) central to the pathogenesis of psoriasis may play a role. The mechanism by which STELARA may induce paradoxic psoriasis is not known.

Evidence source(s) and strength of evidence:

Pustular psoriasis has been reported in ustekinumab clinical trials and in the postmarketing setting. Some of the postmarketing reports suggest a causal relationship with STELARA based on temporal relationship, recurrence with re-challenge, and presence of the rare palmoplantar pattern. Pustular psoriasis is considered an ADR for STELARA (SmPC section 4.8 [Undesirable Effects] and Package Leaflet section 4).

Characterization of the risk – Data:

Table SVII.3: Important Identified Risk - Pustular Psoriasis; 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	79.1	11.5	107.0
Frequency[b]										
Ustekinumab vs	<0.1% vs	0.1% vs	0.3% vs	0.4% vs	0.0% vs	0.1% vs	0.0% vs	0.0% vs	0.1% vs	0.1% vs
Placebo/Comparator[c]	0.1%	0.1%	0.3%	0.3%	0.0%	0.2%	0.0%	0.0%	0.1%	0.1%
Odds ratio (95% CI)	-	-	-	-	-	-	-	-	-	-
Seriousness/outcomes										
Was Serious	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%)
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	1 (<0.1%)	4 (0.1%)	1 (0.1%)	3 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (<0.1%)	7 (0.1%)
Did not recover (Persisted)	0 (0.0%)	1 (<0.1%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (<0.1%)	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	1 (<0.1%)	4 (0.1%)	2 (0.3%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.1%)	6 (0.1%)
Moderate	0 (0.0%)	1 (<0.1%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (<0.1%)
Severe	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%)
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 96 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)
Note: Pustular psoriasis is identified by MedDRA Preferred Terms of Pustular psoriasis and Palmoplantar pustulosis.

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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/PSUR 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 identified risk of 'Pustular psoriasis.'

The impact of a pustular psoriasis on the individual patient can vary from minimal to severe, depending on the form of pustular psoriasis. It can be localized or a more clinically severe generalized form, accompanied by fever lasting several days. Pustular psoriatic outbreaks are serious and require aggressive treatment but will likely resolve shortly after discontinuation of STELARA. The rare, acute generalized type of pustular psoriasis can be life threatening, so hospitalization and supportive care is usually required. Pustular psoriasis can be fatal in rare cases.

Risk factors and risk groups:

Pustular psoriasis can occur *de novo* or may be triggered in certain settings (Kole et al, 2012). Factors that could trigger pustular psoriasis include internal medications, irritating topical agents, overexposure to ultraviolet (UV) light, pregnancy, systemic steroids, infections, emotional stress, and sudden withdrawal of systemic medications or potent topical steroids (National Psoriasis Foundation 2014). There have been case reports of pustular psoriasis in CD patients exposed to anti-TNF treatment (Steinwurz et al 2012).

Preventability:

The predictability and preventability of pustular psoriasis is not known.

No testing is available to identify at-risk patients.

Impact on the risk-benefit balance of the product:

Cases of pustular psoriasis are infrequently reported in association with ustekinumab use and are not likely to have a significant negative impact on the risk-benefit balance of the product.

Further characterization of the incidence and risk factors for pustular psoriasis is conducted through routine pharmacovigilance activities and registries.

Public health impact:

The potential public health impact is not known.

MedDRA term for Annex 1:

Preferred term (PT): Pustular psoriasis.

Important identified risk – Erythrodermic psoriasis

Potential mechanisms:

Some patients treated with STELARA developed a rare type of psoriasis called erythrodermic psoriasis. It may arise from any form of psoriasis and can occur as a spontaneous generalization of plaque or pustular psoriasis or may be the initial manifestation of psoriasis.

Erythrodermic psoriasis results from disease progression or generalization of a pre-existing dermatosis. It can also occur with the drugs used to treat psoriasis.

The mechanism by which STELARA may induce erythrodermic psoriasis is not known. However, paradoxic worsening and new-onset of erythrodermic psoriasis have been described with other biologics including TNFα inhibitors (eg, rituximab, efalizumab, and anakinra). One theory postulates disruption in cytokine balance induced by TNF blockade may allow for unopposed interferon-α production by plasmacytoid dendritic cells in genetically predisposed individuals. Plasmacytoid dendritic cells are found in the normal skin of psoriasis patients, in early psoriatic plaques, and in patients with other inflammatory autoimmune disease. Another theory suggests that alternative key cytokines (eg, IL-17 and IL-22) central to the pathogenesis of psoriasis may play a role.

Evidence source(s) and strength of evidence:

The clinical data in psoriasis and PsA showed no imbalance in ustekinumab-treated patients compared with placebo, no evidence of a dose response, and very few adverse events (AEs) overall. Postmarketing reports of new-onset erythrodermic psoriasis have been received; most cases included confounding elements (eg, a triggering element was noted, the diagnosis was in question, or ustekinumab was continued with resolution). Literature evidence is inconclusive since some support the use of ustekinumab in patients with erythrodermic psoriasis, while others reported AEs of erythrodermic psoriasis and exfoliative dermatitis after the use of ustekinumab. Therefore, based on postmarketing reports of erythrodermic psoriasis, it was included as an ADR for STELARA (SmPC section 4.8 [Undesirable Effects] and Package Leaflet section 4).

Characterization of the risk – Data:

Table SVII.4: Important Potential Risk - Erythrodermic Psoriasis; 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	79.1	11.5	107.0
Frequency[b]										
Ustekinumab vs	0.0% vs	<0.1% vs	0.1% vs	0.1% vs	0.0% vs	0.0% vs	0.0% vs	0.0% vs	<0.1% vs	<0.1% vs
Placebo/Comparator[c]	0.1%	0.1%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	<0.1%	0.1%
Odds ratio (95% CI)	-	-	-	-	-	-	-	-	-	-
Seriousness/outcomes										
Was Serious	0 (0.0%)	1 (<0.1%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (<0.1%)	2 (<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%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (<0.1%)	1 (<0.1%)
Did not recover (Persisted)	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%)
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%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	1 (<0.1%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (<0.1%)	2 (<0.1%)
Severe	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%)

[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 96 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/PSUR 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 identified risk of 'Erythrodermic psoriasis.'

No cases of erythrodermic psoriasis were reported in clinical trials conducted for indications other than psoriasis and PsA through the data lock point.

The impact of erythrodermic psoriasis on the individual patient is often severe because the condition affects a large part of the body surface. Erythrodermic psoriasis is serious and requires hospitalization with aggressive treatment in all cases. The episode will resolve shortly after the elimination of triggers and use of appropriate therapeutics.

Risk factors and risk groups:

Abrupt withdrawal of systemic or potent topical steroids; unstable psoriasis; trauma; infections; drugs such as lithium, anti-malarial medications, trimethoprim, and sulfamethoxazole; withdrawal of systemic glucocorticoid or other immunomodulating agents; and environmental, psychological, and metabolic factors can trigger psoriasis and the erythrodermic form of the disease (Dika et al 2007; Fry and Baker 2007). There have been case reports of pustular psoriasis in CD patients exposed to anti-TNF treatment (Steinwurz et al 2012; Lawley et al 2012).

Erythrodermic psoriasis has been noted to appear often in people who have unstable plaque psoriasis (www.psoriasis.org).

Preventability:

The preventability of erythrodermic psoriasis is not known.

No testing is available to identify at-risk patients.

Impact on the risk-benefit balance of the product:

Cases of erythrodermic psoriasis are infrequently reported in association with ustekinumab use and are not likely to have a significant negative impact on the risk-benefit balance of the product.

Further characterization of the incidence and risk factors for erythrodermic psoriasis is conducted through routine pharmacovigilance activities and registries.

Public health impact:

Erythrodermic psoriasis occurs once or more during the lifetime of 3% of people with psoriasis (www.psoriasis.org).

The potential public health impact is not known.

MedDRA term for Annex 1:

PT: Erythrodermic psoriasis.

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 et al 2005), *Mycobacterium tuberculosis* (Khader et al 2005), *Cryptococcus neoformans* (Kleinschek et al 2006), and *Candida albicans* (Acosta-Rodriguez et al 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 and Casanova 2003; Novelli and Casanova 2004). Filipe-Santos et al (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 infection (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.

Characterization of the risk – Data:

Table SVII.5: 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	79.1	11.5	107.8
Frequency[b]										
Ustekinumab vs	0.4% vs	2.5% vs	0.0% vs	1.4% vs	1.5% vs	7.2% vs	0.5% vs	4.2% vs	0.6% vs	3.7% vs
Placebo/Comparator[c]	0.4%	0.5%	0.3%	0.3%	1.1%	2.2%	1.3%	2.8%	0.6%	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%)	35 (4.2%)	33 (0.6%)	271 (3.7%)
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%)	33 (4.0%)	33 (0.6%)	258 (3.6%)
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%)	23 (2.8%)	13 (0.3%)	113 (1.6%)
Severe	8 (0.3%)	61 (1.7%)	0 (0.0%)	8 (0.8%)	9 (0.6%)	69 (3.8%)	1 (0.2%)	11 (1.3%)	18 (0.4%)	149 (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 96 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.6: 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	79.1	11.5	107.0
Frequency[b]										
Ustekinumab vs	0.0% vs	<0.1% vs	0.0% vs	0.0% vs	0.0% vs	0.1% vs	0.0% vs	0.2% vs	0.0% vs	0.1% vs
Placebo/Comparator[c]	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	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 96 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.7: Important Potential Risk - Serious Infections; Treated Subjects Across Pediatric Psoriasis Studies

	Pediatric Psoriasis Studies[a]	
	All Randomized, Controlled Portions Blinded Trials Population (N=73)	All Clinical Trials Population (N=154)
Avg duration of follow-up (weeks)	12.3	53.2
Frequency[b]		
Ustekinumab vs Placebo/Comparator[c]	0.0% vs 0.0%	1.9% vs 0.0%
Odds ratio (95% CI)	-	-
Seriousness/outcomes		
Was Serious	0 (0.0%)	3 (1.9%)
Resulted in Death	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	3 (1.9%)
Did not recover (Persisted)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)
Severity		
Mild	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	3 (1.9%)
Severe	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)

[a] Pediatric psoriasis studies include CNTO1275PSO3006 and CNTO1275PSO3013.
[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:
All Randomized, Controlled Portions Blinded Trials Population (N=37), 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 PBRER/PSUR 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 infection (including mycobacterial and salmonella infections).' No safety signal has been observed.

The impact of serious infection on the individual patient may be significant. Patients with a history of latent TB will require additional therapy prior to using STELARA or will have to choose a medication other than STELARA. Patients with active infections will have to choose an alternative medication and discontinue use of STELARA until the infection is cleared. Patients who develop infections may potentially have a more severe course 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:

Serious infections

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

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: 1.0-4.5) and age >50 years (OR=26.5; 95% CI: 10.9-67.3; O'Brien et al 2000). Similarly, in a US study (Cassidy et al 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 et al 2013). Prolonged occupational exposure to soil was an important risk factor for MAC infection in a US study (Reed et al 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: Salmonella Infection Risk Factors).

Preventability:

STELARA is contraindicated in patients with a clinically important, active infection (eg, active TB) (SmPC section 4.3 [Contraindications]).

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.

MedDRA term for Annex 1:

SOC: Infections and infestations.

Important potential risk – Malignancy

Potential mechanisms:

Scientific literature suggests that IL-12 can contribute to tumor immunosurveillance (Colombo and Trinchieri 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 et al 1997). Cárdenes et al (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 2 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 considered an important potential risk.

Characterization of the risk – Data:

Table SVII.8: 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	79.1	11.5	107.0
Frequency[b]										
Ustekinumab vs	0.2% vs	1.3% vs	0.1% vs	0.4% vs	0.0% vs	0.7% vs	0.0% vs	0.7% vs	0.1% vs	0.9% vs
Placebo/Comparator[c]	0.1%	0.1%	0.0%	0.0%	0.0%	0.2%	0.0%	0.0%	0.1%	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%)	6 (0.7%)	5 (0.1%)	62 (0.8%)
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%)	2 (0.2%)	4 (0.1%)	32 (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 96 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.9: 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	79.1	11.5	107.0
Frequency[b]										
Ustekinumab vs	0.1% vs	1.5% vs	0.0% vs	0.3% vs	0.0% vs	0.7% vs	0.0% vs	0.6% vs	0.1% vs	1.0% vs
Placebo/Comparator[c]	0.1%	0.1%	0.0%	0.0%	0.0%	0.2%	0.0%	0.6%	<0.1%	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%)	4 (0.5%)	2 (<0.1%)	65 (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%)	5 (0.6%)	0 (0.0%)	37 (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%)	0 (0.0%)	1 (<0.1%)	12 (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%)	4 (0.5%)	1 (<0.1%)	41 (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 96 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/PSUR 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 has been observed. 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 et al 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 the 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 non-melanoma 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.

MedDRA term for Annex 1:

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 et al 2006). The greatest risk of myocardial infarction (MI) is found in young patients with severe psoriasis (Gelfand et al 2006). As in psoriasis, patients with PsA are reported to be at increased risk for occlusive vascular diseases, including MI and stroke (Husted et al 2011; Tobin et al 2010; Li et al 2012; Gladman et al 2009). 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 event (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 2 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.10: 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	79.1	11.5	107.0
Frequency[b]										
Ustekinumab vs	0.2% vs	1.0% vs	0.0% vs	1.0% vs	0.0% vs	0.4% vs	0.0% vs	0.6% vs	0.1% vs	0.8% vs
Placebo/Comparator[c]	0.0%	0.1%	0.3%	0.3%	0.0%	0.2%	0.3%	0.3%	0.1%	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%)	30 (0.8%)	0 (0.0%)	7 (0.7%)	0 (0.0%)	5 (0.3%)	0 (0.0%)	3 (0.4%)	4 (0.1%)	45 (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%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (<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 96 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/PSUR 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 has been observed.

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 in adequate treatment of CV risk factors. The impact of MACE on the individual patient may be very significant. Events of MACE may result in fatal outcome.

Risk factors and risk groups:

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

Preventability:

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

Impact on the risk-benefit balance of the product:

Although MACEs 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 MACEs 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 MACE is conducted through routine pharmacovigilance activities and registries.

Public health impact:

The potential public health impact is not known.

MedDRA term for Annex 1:

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 Package Leaflet 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.11: 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	79.1	11.5	107.0
Frequency[b]										
Ustekinumab vs	0.0% vs	0.2% vs	0.1% vs	0.4% vs	0.1% vs	0.4% vs	0.0% vs	0.1% vs	0.1% vs	0.3% vs
Placebo/Comparator[c]	0.0%	0.0%	0.3%	0.5%	0.0%	0.2%	0.0%	0.0%	<0.1%	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 96 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/PSUR 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 has been observed.

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 and Kravitz 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.

MedDRA term for Annex 1:

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

Important potential risk – Reversible Posterior Leukoencephalopathy Syndrome

Potential mechanisms:

The pathophysiology of RPLS (also known as Posterior Reversible Encephalopathy Syndrome [PRES]) is not well understood. It is currently believed to be caused by disordered autoregulation of cerebral blood flow and/or endothelial dysfunction, resulting in disruption of the blood-brain barrier and edema (Allen et al 2006). An important part of the diagnosis includes neuroimaging, preferably magnetic resonance imaging, as the clinical presentation may be nonspecific.

The mechanism by which STELARA could cause RPLS is not known.

Evidence source(s) and strength of evidence:

Two cases of RPLS were reported in clinical trials, only 1 of which was in an approved indication (psoriasis). Events of RPLS have been reported in the postmarketing setting, including individual reports in the literature, but there is no evidence for causal association or mechanistic or scientific evidence for causality.

Characterization of the risk – Data:

Table SVII.12: Important Potential Risk - Reversible Posterior Leukoencephalopathy Syndrome; 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	79.1	11.5	107.0
Frequency[b]										
Ustekinumab vs	0.0% vs	<0.1% vs	0.0% vs	0.0% vs	0.0% vs	0.0% vs	0.0% vs	0.0% vs	0.0% vs	<0.1% vs
Placebo/Comparator[c]	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Odds ratio (95% CI)	-	-	-	-	-	-	-	-	-	-
Seriousness/outcomes										
Was Serious	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%)
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%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (<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%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	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%)
Severe	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%)
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 96 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/PSUR 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 'Reversible posterior leukoencephalopathy syndrome.' No safety signal has been observed.

In addition to the 1 case of RPLS reported above (Table SVII.12), a second case has been reported in an ustekinumab clinical trial (CNTO1275SLE2001) in an unapproved indication. This case of RPLS was reported in a subject with systemic lupus erythematosus (SLE) and was considered to be confounded by the subject's lupus nephritis and poorly controlled hypertension. Importantly, clinical evidence suggests a strong independent association of SLE with RPLS and the subject was suffering from an SLE exacerbation at the time of the event. The event of RPLS occurred approximately 3 months after the subject took the last dose of ustekinumab.

The impact of RPLS on the individual patient may vary from minor to significant, and the symptoms usually resolve with timely treatment. Patients with RPLS typically present with headache, confusion, visual disturbance, and seizures. These symptoms are rapid in onset, often associated with elevations in blood pressure, and are usually reversible, although the syndrome can be serious. Fatalities have been reported.

Risk factors and risk groups:

Reversible posterior leukoencephalopathy syndrome has been associated with diverse clinical scenarios including hypertensive encephalopathy, pre-eclampsia, renal failure, electrolyte abnormalities, rheumatologic diseases (including SLE), and cytotoxic and immunosuppressant drugs. Case reports in the literature have cited possible association with multiple drugs including cyclosporin, MTX, tacrolimus (Prograf), rituximab (Rituxan), bevacizumab (Avastin), bortezomib (Velcade), and some TNF blockers (Avastin® [Prescribing Information] 2009; Bartynski 2008; Hinchey et al 1996; Kastrup and Diener 2008; Kur 2006; Lee et al 2008; Rajasekhar and George 2007; Velcade® [Prescribing Information] 2008; Zamvar et al 2009).

Preventability:

There are no known means of preventing RPLS. No testing is available to identify at-risk patients.

Impact on the risk-benefit balance of the product:

Although 'Reversible posterior leukoencephalopathy syndrome' 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 RPLS 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 'Reversible posterior leukoencephalopathy syndrome' is conducted through routine pharmacovigilance activities and registries.

Public health impact:

The potential public health impact is not known.

MedDRA term for Annex 1:

PT: Posterior reversible encephalopathy syndrome.

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 et al 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 2 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 1-8% reported in the IBD literature (Alkim et al 2017; Danese et al 2007; Nguyen et al 2014).

Overall, safety results from the CD clinical trials through Week 272, UC trials through Week 96, and from 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.13: 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	79.1	11.5	107.0
Frequency[b]										
Ustekinumab vs	<0.1% vs	0.4% vs	0.0% vs	0.1% vs	0.2% vs	0.9% vs	0.3% vs	1.0% vs	0.1% vs	0.6% vs
Placebo/Comparator[c]	0.0%	0.0%	0.0%	0.0%	0.2%	0.5%	0.0%	0.0%	<0.1%	0.1%
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 96 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/PSUR 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 has been observed.

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 et al 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 et al 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, and the highest risk of VTE was in the 0 to 20 years age group with an HR of 6.6 (95% CI: 3.3-13.2) compared with 1.6 (95% CI: 1.5-1.8) for the ≥60 years age group (Kappelman et al 2011). 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: 1.14-10.5) and 2.97 (95% CI: 0.99-8.92), respectively (Vegh et al 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.

MedDRA term for Annex 1:

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

Important potential risk – Exposure during pregnancy

Potential mechanisms:

Toxicokinetic analyses have confirmed that ustekinumab can cross the placenta; however, nonclinical studies have shown no effect.

The effects of exposure to STELARA on the developing fetus are not known.

Evidence source(s) and strength of evidence:

The effects of ustekinumab during pregnancy are not known.

Toxicokinetic analyses have confirmed that ustekinumab can cross the placenta; however, nonclinical studies have shown no effect. Cumulative safety data do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition, or postnatal development (SmPC section 4.6 [Fertility, pregnancy and lactation]), but cases of exposure during pregnancy are limited.

'Exposure during pregnancy' is considered an important potential risk because of the limitations of nonclinical investigations on this topic and the limited data in humans related to exposure during pregnancy.

Characterization of the risk – Data:

Table SVII.14: Pregnancy Outcomes for Ustekinumab Medically Confirmed Cases With Maternal Exposure Cumulatively Through 31 December 2019 (n=1,720)

Pregnancy Outcome[a]	Clinical Trial						Spontaneous/ Solicited	Total
	PSO	PsA	CD	UC	Others[b]	Total		
Live birth	**17**	**0**	**18**	**8**	**2**	**45**	**514**	**559**
Congenital anomaly/birth defect[c]	0	0	0	0	0	**0**	21	**21**
Other AEs[d]	2	0	0	1	0	**3**	31	**34**
No AE/congenital anomaly/birth defect[e]	14	0	16	7	2	**39**	437	**476**
Premature birth	1	0	2	0	0	**3**	25	**28**
Spontaneous abortion	5	0	5	3	0	**13**	147	**160**
Elective/induced abortion/ abortion scheduled	10	1	7	1	0	**19**	49	**68**
Abortion (unspecified/missed)	0	0	0	0	1	**1**	4	**5**
Ectopic pregnancy	2	0	0	0	0	**2**	3	**5**
Intrauterine/ neonatal demise	0	0	0	0	0	**0**	5	**5**
NR/continuing	6	1	5	0	0	**12**	915[f]	**927**
Total[g]	**40**	**2**	**35**	**12**	**3**	**92**	**1,637**[h]	**1,729**

Note: Interventional clinical trial protocol numbers: CNTO1275CRD3003, C0743T09, CNTO1275UCO3001, C0743T08, CNTO1275CRD3005, CNTO1275PSO3009, C0743T12, CNTO1275PSO4004, CNTO1275NAP1002, CNTO1275PSO3006, C0743T26, C0379T04, CNTO1275PSA3001, C0743T23, CNTO1275CRD3001, CNTO1275PSO4039, C0743T06, C0743T10, CNTO1275CRD3006, CNTO1275CRD4008

Non-interventional clinical trial protocol numbers: RRA-5319, CNTO1275PSO4037, MCO-C127-040, C0168Z03, RRA-10836, RRA-1725, NONCOMPSTUDY_USTEKIN, RRA-15143, RRA-6577, RRA-8541, RRA-7583, RRA-19442, RRA-6660, RRA-15248, RRA-10142, RRA-11525, CNTO1275CRD4007, PPSIMM000643, PPSIMM000812, CNTO1275CRD4028, RRA-18356, STL1L, CNTO1275PSO4058, RRA-3422, CNTO1275PSO4011, PPSIMM000173, CNTO1275PSO4051, CNTO1275CRD4018, RRA-21341, SPECTRUM, RRA-4060, NONCOMPSTUDY_INFLIX, RRA-21224, RRA-11632, RRA-14093, RRA-718, RRA-21470, RRA-19567, RRA-18375, CNTO1275PSO4003, CNTO1959PSO4001, PPSIMM000231, JS2018-19413, CNTO1275CRD4006, CNTO1275PSO3007, BIOBADASER, RRA-19613, RRA-9032, PPSIMM000896, CNTO1275PSO4057, PPSIMM001410, RRA-17465, PPSIMM000647, CNTO1275PSO4031, CNTO1275PSO4028, JOPC2018-19603, RRA-7476, STEL-JJPAF, CNTO1275PSO4033, CNTO1275CRD4002, RRA-9440, RRA-16471, CNTO1275CRD4003, CNTO1275IBD4001, RRA-16437, RRA-16446

Key: AE=Adverse Event; CD=Crohn's Disease; n=Number; NR=Not Reported; PsA=Psoriatic Arthritis; PSO=Psoriasis; UC=Ulcerative Colitis.

[a] A single case may report more than 1 pregnancy outcome.

[b] Other includes cases in relapsing-remitting multiple sclerosis and drug level.

[c] Count includes 3 cases reporting premature birth, including 1 twin pregnancy case.

[d] Count for spontaneous/solicited cases includes 7 cases reporting premature birth.

[e] Count for spontaneous/solicited cases includes 5 cases reporting twin pregnancy.

[f] Count includes 2 cases reporting spontaneous abortion and 1 case reporting a twin pregnancy.

[g] Case counts include cases from long-term extension portions of the Crohn's disease study (CRD3003).

[h] Count includes cases from non-interventional clinical trial studies.

Table SVII.15: Pregnancy Outcomes for Ustekinumab Medically Confirmed Cases With Paternal Exposure Cumulatively Through 31 December 2019 (n=336)

Pregnancy Outcome	Clinical Trial						Spontaneous/ Solicited	Total
	PSO	PsA	CD	UC	Other[a]	Total		
Live birth	**41**	**0**	**7**	**5**	**0**	**53**	141	**194**
Congenital anomaly/birth defect	1	0	0	0	0	**1**	5	**6**
Other AEs	4	0	0	0	0	**4**	11[b]	**15**
No AE/congenital anomaly/birth defect	31	0	7	5	0	**43**	115[c]	**158**
Premature birth	5[d]	0	0	0	0	**5**	10	**15**
Elective abortion	1	0	1	0	0	**2**	3	**5**
Spontaneous abortion	3	1	3	0	0	**7**	8	**15**
Intrauterine/neonatal demise	0	0	0	0	0	**0**	2	**2**
NR/continuing	5	2	4	1	5	**17**	104[e]	**121**
Total[f]	**50**	**3**	**15**	**6**	**5**	**79**	**256[g]**	**335**

Note: Interventional clinical trial protocol numbers: C0743T09, C0743T08, CNTO1275CRD3003, CNTO1275UCO3001, CNTO1275PSA3001, C0743T12, C0379T07, CNTO1275CRD3005, CNTO1275AKS3001, CNTO1275PSO3009, C0379T04, C0743T25, CNTO1275AKS3002, C0743T23, CNTO1275CRD3001, C0743T11, C0743T06.
Non-interventional clinical trial protocol numbers: C0168Z03, RRA-5319, RRA-10836, CNTO1275PSO4051, RRA-8541, NONCOMPSTUDY_USTEKIN, RRA-6660, RRA-3422, SPECTRUM, JOPC2019-21920, RRA-19442, CNTO1275PSO0002, CNTO1275PSO4016, RRA-10142, CNTO1275CRD4007, CNTO1275PSO3007, CNTO1959PSO4001, RRA-15143.
Key: AE=Adverse Event; CD=Crohn's Disease; n=Number; NR=Not Reported; PsA=Psoriatic Arthritis; PSO=Psoriasis; UC=Ulcerative colitis.
[a] Other includes cases where indication was not reported and the case where study was a pharmacokinetic study.
[b] Count also includes 1 case reporting a twin pregnancy.
[c] Count also includes 1 case reporting a twin pregnancy.
[d] Count also includes 2 twin pregnancy cases.
[e] Count includes 1 case which reported that the baby underwent cardiac surgery immediately after birth.
[f] Case counts include cases from long-term extension portion of the Crohn's disease study (CRD3003).
[g] Count includes cases from non-interventional clinical trial studies also.

Characterization of the risk – Discussion:

The global safety database was searched for medically confirmed and medically unconfirmed cases through the data lock point that may have involved exposure during pregnancy or lactation. Based on the review of the data to date, no new safety information was identified for the important potential risk of 'Exposure during pregnancy.' No safety signal has been observed.

One pregnancy was reported in the pediatric psoriasis clinical trial (CNTO1275PSO3006) through the data lock point.

The effects of ustekinumab during pregnancy are not known. Toxicology studies indicate that ustekinumab crosses the placenta, however, nonclinical studies have shown no negative effect on the pregnant females or any fetal abnormalities. The potential risk needs to be carefully weighed against the benefit conferred by use of the medication.

See Table SIV.2 for details regarding the reported exposures during pregnancy for STELARA.

Risk factors and risk groups:

Patients who do not follow guidance on use of contraception or use contraception incorrectly are at risk for pregnancy. Most of the systemic antipsoriatic therapies are associated with significant toxic effects to the fetus and are recommended to be avoided during pregnancy (Landau et al 2011).

A recent update on the safety of IBD medications in pregnancy summarized that the available data provide reassuring information for providers caring for women with IBD and of childbearing age, although long-term effects of IBD medications on offspring need to be examined (Damas et al 2015).

Preventability:

As a precautionary measure, it is preferable to avoid the use of STELARA in pregnancy. Women of childbearing potential should use effective methods of contraception during treatment and up to 15 weeks after treatment (SmPC section 4.6 [Fertility, Pregnancy and Lactation]). STELARA should be given to a pregnant woman only if the benefit clearly outweighs the risk.

Impact on the risk-benefit balance of the product:

The impact of drug exposure during pregnancy on the patient and the fetus is unknown and thus the impact of this risk on the risk-benefit balance of STELARA is unclear.

Public health impact:

The potential public health impact is not known.

MedDRA term for Annex 1:

HLT: Exposures associated with pregnancy, delivery, and lactation.

SVII.3.2. Presentation of the Missing Information

Missing information: Use in patients with a history of latent tuberculosis or tuberculosis
Evidence source: Patients with a history of adequately treated active or latent TB were eligible for inclusion in the clinical program. Patients with previously untreated latent TB were eligible so long as they were given therapy during the trial.
Anticipated risk/consequence of the missing information: Due to its mechanism of action, STELARA may affect how a patient reacts to TB bacteria (ie, it may inhibit protective immune responses to intracellular bacteria, including mycobacteria). The risk to patients with a history of latent TB or TB is not fully known. The current safety information from clinical trials and postmarketing experience has not shown a safety concern. People who were treated for latent inactive TB while taking STELARA did not appear to be at increased risk of TB reactivation. Patients with active TB have not been studied.

Missing information: Use in patients with concurrent malignancy or a history of malignancy
Evidence source: Nonclinical studies suggest that IL-12 may contribute to tumor immunosurveillance and/or tumor-directed cytotoxic T-cell responses (see Module SII). Patients with any known malignancy or history of malignancy (except basal cell carcinoma, squamous cell carcinoma in situ of the skin, or cervical carcinoma in situ that has been treated with no evidence of recurrence, or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years prior to first treatment with STELARA) were excluded from the Phase 3 psoriasis, PsA, and CD trials.
Population in need of further characterization: Patients with concurrent malignancy or a history of malignancy other than NMSC.

Missing information: Use in patients with recent or concomitant use of immunosuppressive therapy other than methotrexate, 6-mercaptopurine, azathioprine, 5-aminosalicylic acid, and corticosteroids
Evidence source: Exposure in patients with recent or concomitant use of immunosuppressive therapy other than MTX, 6-MP, AZA, 5-ASA, and corticosteroids is presented in Table SIV.2. The current available safety data in patients with the use of ustekinumab and concomitant MTX, prednisone, cyclosporin, and AZA have not shown a safety concern. However, the MAH cannot exclude the possibility that use of STELARA in this patient population could lead to more profound immunosuppression and thus a novel safety concern or exacerbation of an existing safety concern.
Population in need of further characterization: Patients with recent or concomitant use of immunosuppressive therapy other than MTX, 6-MP, AZA, 5-ASA, and corticosteroids.

Missing information: Long-term safety in pediatric psoriasis patients 6 years and older
Evidence source: Trial CNTO1275PSO3006 and the main study for trial CNTO1275PSO3013 investigated the use of ustekinumab in pediatric psoriasis patients 6 years and older through 60 weeks and 56 weeks, respectively. The long-term extension for CNTO1275PSO3013 is ongoing and will continue through up to 264 weeks.
Population in need of further characterization: Pediatric patients with psoriasis ≥6 years of age with long-term exposure to STELARA.

Missing information: Long-term impact on growth and development in pediatric psoriasis patients 6 years and older
Evidence source: Trial CNTO1275PSO3006 and the main study for trial CNTO1275PSO3013 investigated the use of ustekinumab in pediatric psoriasis patients 6 years and older through 60 weeks and 56 weeks, respectively. The long-term extension for CNTO1275PSO3013 is ongoing and will continue through up to 264 weeks.
Population in need of further characterization: Pediatric patients with psoriasis ≥6 years of age with long-term exposure to STELARA.

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.
Population in need of further characterization: Adults with moderately to severely active CD who have been treated with STELARA beyond maintenance Week 272.

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 maintenance Week 96.
Population in need of further characterization: Adults with moderately to severely active UC who have been treated with STELARA beyond maintenance Week 96.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important identified risks	Serious systemic hypersensitivity reactions
	Facial palsy
	Pustular psoriasis
	Erythrodermic psoriasis
Important potential risks	Serious infections (including mycobacterial and salmonella infections)
	Malignancy
	Cardiovascular events
	Serious depression including suicidality
	Reversible posterior leukoencephalopathy syndrome
	Venous thromboembolism
	Exposure during pregnancy
Missing information	Use in patients with a history of latent tuberculosis or tuberculosis
	Use in patients with concurrent malignancy or a history of malignancy
	Use in patients with recent or concomitant use of immunosuppressive therapy other than methotrexate, 6-mercaptopurine, azathioprine, 5-aminosalicylic acid, and corticosteroids
	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

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

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

Specific Follow-up Questionnaires for Safety Concerns

Safety Concern	Purpose/Description
Serious systemic hypersensitivity reactions	Targeted follow-up questionnaire (TFUQ) to collect information on hypersensitivity
Facial palsy	TFUQ to collect information on facial palsy (Bell's Palsy)
Pustular psoriasis, Erythrodermic psoriasis	TFUQ to collect information on psoriasis variant (pustular, erythrodermic, guttate)
Serious infections (including mycobacterial and salmonella infections)	TFUQ to collect information on serious infections and opportunistic infections and TFUQ to collect information on tuberculosis
Malignancy	TFUQ to collect information on malignancies and TFUQ to collect information on lymphoma
Cardiovascular events	TFUQ to collect information on cardiovascular events
Reversible posterior leukoencephalopathy syndrome	TFUQ to collect information on reversible posterior leukoencephalopathy syndrome
Venous thromboembolism	TFUQ to collect information on venous thromboembolism

Other Forms of Routine Pharmacovigilance Activities

Activity	Objective/Description	Milestones
Not applicable	Not applicable	Not applicable

III.2. Additional Pharmacovigilance Activities

Additional Pharmacovigilance Activities	
Trial/Registry/Study	
Registry name and title	C0168Z03 PSOLAR (plaque psoriasis [overlapping forms of psoriasis may be included]): A multicenter, prospective, observational registry of patients with psoriasis who are candidates for systemic therapy including biologics.
Rationale and registry objectives	The objective of this registry is to evaluate the safety of STELARA in patients with moderate to severe plaque psoriasis (plaque psoriasis [overlapping forms of psoriasis may be included]). To address the safety concerns of: • Serious systemic hypersensitivity reactions • Facial palsy • Pustular psoriasis • Erythrodermic psoriasis • Serious infections (including mycobacterial and salmonella infections) • Malignancy • Cardiovascular events • Serious depression including suicidality • Reversible posterior leukoencephalopathy syndrome • Use in patients with a history of latent tuberculosis or tuberculosis • Use in patients with concurrent malignancy or a history of malignancy • Use in patients with recent or concomitant use of immunosuppressive therapy other than methotrexate, 6-mercaptopurine, azathioprine, 5-aminosalicylic acid, and corticosteroids
Registry design	PSOLAR is a multicenter, prospective, longitudinal, observational registry study of long-term safety and clinical outcomes in patients receiving treatment for psoriasis in academic and community-based clinical practices.
Registry population	The registry population is psoriasis patients (plaque psoriasis [overlapping forms of psoriasis may be included]) who are eligible to receive systemic therapies, including generalized phototherapy and biologics in actual clinical use.
Milestones	Protocol submission: 25 June 2009 Registry start: 20 June 2007 First patient in was 20 June 2007 which is prior to the protocol submission date because this registry was initially a REMICADE registry. The registry was expanded to include STELARA patients on 19 March 2009 and the first STELARA patient was enrolled in PSOLAR on 24 March 2009. Registry finish: 06 September 2021 Final report: 30 June 2022

Additional Pharmacovigilance Activities	
Trial/Registry/Study	
Registry name and title	CNTO1275PSO4007 (Pregnancy Research Initiative): Exposure to ustekinumab during pregnancy: A review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers.
Rationale and registry objectives	The objectives of this registry are to the collection and analysis of information pertaining to pregnancy outcomes of women who were exposed to ustekinumab during pregnancy and health status in the first year of life of infants born to women following prenatal exposure to STELARA compared with controls. To address the safety concern of: • Exposure during pregnancy
Registry design	CNTO1275PSO4007 is a prospective, observational, exposure-based, cohort registry analyzing birth and infant outcome data obtained from the national Swedish Medical Birth Register, Danish Medical Birth Register, and the Finnish Medical Birth Register for all women who were exposed to ustekinumab during pregnancy and up to 3 months prior to their last menstrual period (LMP) and their infants. The health status of the infants born to these women will be followed prospectively for 1 year after birth.
Registry population	The study includes women who were exposed to ustekinumab for any reason (ie, authorized indications, off-label use, or unknown/missing use) at any time during pregnancy and up to 3 months prior to their LMP. The following other cohorts are also included: women who have any condition for which ustekinumab is authorized for use (ie, a disease of interest) and have documented exposure to biologic agents other than ustekinumab at any time during pregnancy and up to 3 months prior to LMP, women who have a disease of interest and have received systemic therapy other than biologic agents at any time during pregnancy and up to 3 months prior to LMP, and women who do not have a disease of interest and have not received treatment with a biologic or non-biologic systemic therapy at any time during pregnancy and up to 3 months prior to the LMP. The infants of the women included in each cohort are also included in the registry.
Milestones	Protocol submission: 25 June 2009 Registry start: 20 July 2009 Registry finish: 15 December 2020 Final report: 01 December 2021
Registry 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

Additional Pharmacovigilance Activities	
Trial/Registry/Study	
Rationale and registry objectives	The objective of this registry 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. 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.
Registry design	CNTO1275PSO4056 is a prospective, observational, international, multicenter registry to monitor the long-term safety and potential impact on growth and development of ustekinumab in the treatment of pediatric psoriasis within clinical practice. Only data available within clinical practice will be collected. Additionally, where local regulations permit, data on clinical skin response (Psoriasis Area and Severity Index, Physician Global Assessment of Disease, and BSA), quality of life, and information relating to growth and development will be obtained. Patients will be followed for 8 years or until the age of 18, whichever occurs first, or until early withdrawal or study closure.
Registry population	Patients with psoriasis who are 6 years of older and meet all eligibility criteria may be enrolled. Participating patients will be enrolled at dermatology centers, practices, and hospital outpatient departments with expertise in the use of biologics and systemic therapies in the treatment of pediatric psoriasis.
Milestones	Protocol submission: 21 December 2015 Registry start: 25 October 2017 Registry finish: 31 August 2032 Final report: 31 March 2033
Study name and title	RRA-20745: An observational postauthorization safety study to describe the safety of ustekinumab and other Crohn's disease treatments in a cohort of patients with Crohn's disease
Rationale and study objectives	The objective of this study is to monitor the long-term safety profile of STELARA use in adult patients with moderately to severely active CD. To address the safety concerns of: • Venous thromboembolism • Long-term safety in adult patients with moderately to severely active Crohn's disease.
Study design	RRA-20745 is an observational, postauthorization safety study to describe the safety profile of adult patients with CD. This study will constitute secondary use of data from patients enrolled into the independent I-CARE study (a prospective, observational, multicenter cohort study).

Additional Pharmacovigilance Activities	
Trial/Registry/Study	
Study population	This study includes patients who receive ustekinumab treatment and those receiving other CD treatments within routine clinical practice, using data collected in the I-CARE trial.
Milestones	Protocol submission: 27 September 2017 Start of data collection: 31 December 2019 End of data collection: 30 September 2022 Final report: 30 September 2023
Trial name and title	Long-term extension of trial CNTO1275UCO3001 (A Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter protocol to evaluate the safety and efficacy of ustekinumab induction and maintenance therapy in subjects with moderately to severely active UC)
Rationale and trial objectives	The objective of the LTE of trial CNTO1275UCO3001 is to evaluate the long-term safety of ustekinumab in adult patients with moderately to severely active UC from maintenance Week 44 through Week 220. To address the safety concern of: • Long-term safety in adult patients with moderately to severely active ulcerative colitis
Trial design	The LTE phase of trial CNTO1275UCO3001 follows eligible subjects for an additional 3 years after completion of the maintenance phase of the trial through Week 44. Subjects in the LTE received induction treatment with either IV ustekinumab or placebo (induction phase of the trial) and then received maintenance treatment with either ustekinumab SC or placebo (maintenance phase of the trial). On entry into the LTE, subjects continued to receive the same treatment regimen that they were receiving at the end of the maintenance phase with the first administered dose at Week 48. Upon completion of the Week 44 maintenance analyses, treatment was unblinded and subjects receiving placebo were terminated from participation in the LTE and subjects receiving ustekinumab continued to receive ustekinumab. During the LTE all subjects were assessed for worsening disease activity and dosage could be adjusted as per protocol.
Trial population	The trial population for the LTE is comprised of the primary population for CNTO1275UCO3001 (ie, subjects with moderately to severely active UC who had an inadequate response to or were intolerant of either conventional or biologic therapy) who had completed the maintenance phase of the trial through Week 44. Subjects who completed the safety and efficacy evaluations at Week 44 of the maintenance study and who may benefit from continued treatment, in the opinion of the investigator, entered the LTE.
Milestones	Protocol submission: January 2019 Trial start: 19 August 2015 (start of induction phase of trial) Trial finish: 31 December 2021 Final report: 31 December 2022

Additional Pharmacovigilance Activities	
Trial/Registry/Study	
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).
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. 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
Study design	This is an observational, postauthorization safety study to describe the safety profile of ustekinumab and other biologic treatments in adult patients with UC or CD. This study uses secondary data from the Swedish Nationwide Healthcare Registers (including the independent Swedish National Quality Register for Inflammatory Bowel Disease [SWIBREG]).
Study population	This study includes UC and CD patients who receive ustekinumab treatment and those receiving other biologic treatments within routine clinical practice.
Milestones	Protocol submission: 23 June 2020 Start of data collection: To be determined End of data collection: 31 August 2026 Final report: 31 March 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)

Additional Pharmacovigilance Activities	
Trial/Registry/Study	
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 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
Study design	This is an observational, postauthorization safety study to describe the safety profile of ustekinumab and other UC treatments in adult patients with UC. This study will constitute secondary use of data from patients as captured in SNDS
Study population	This study includes patients who receive ustekinumab treatment and those receiving other UC treatments within routine clinical practice, using data collected in SNDS
Milestones	Protocol submission: 23 June 2020 Start of data collection: To be determined End of data collection: 31 August 2026 Final report: 30 September 2027

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				

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
C0168Z03 PSOLAR (plaque psoriasis [overlapping forms of psoriasis may be included]): A multicenter, prospective, observational registry of patients with psoriasis who are candidates for systemic therapy including biologics Ongoing	To evaluate the safety of STELARA in patients with moderate to severe plaque psoriasis (plaque psoriasis [overlapping forms of psoriasis may be included]).	• Serious systemic hypersensitivity reactions • Facial palsy • Pustular psoriasis • Erythrodermic psoriasis • Serious infections (including mycobacterial and salmonella infections) • Malignancy • Cardiovascular events • Serious depression including suicidality • Reversible posterior leukoencephalopathy syndrome • Use in patients with a history of latent tuberculosis or tuberculosis • Use in patients with concurrent malignancy or a history of malignancy • Use in patients with recent or concomitant use of immunosuppressive therapy other than methotrexate, 6-mercaptopurine, azathioprine, 5-aminosalicylic acid, and corticosteroids	Protocol submission	25 June 2009
			Registry start	20 June 2007: The trial was expanded to include STELARA patients on 19 March 2009 and the first STELARA patient was enrolled in PSOLAR on 24 March 2009.
			Registry finish	06 September 2021
			Final report	30 June 2022

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
CNTO1275PSO4007 (Pregnancy Research Initiative): Exposure to ustekinumab during pregnancy: A review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers Ongoing	Collection and analysis of information pertaining to pregnancy outcomes of women exposed to STELARA during pregnancy and health status in the first year of life of infants born to women following prenatal exposure to STELARA compared with controls	• Exposure during pregnancy	Protocol submission	25 June 2009
			Registry start	20 July 2009
			Registry finish	15 December 2020
			Final report	01 December 2021
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
			Registry start	25 October 2017
			Registry finish	31 August 2032
			Final report	31 March 2033

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
RRA-20745: An observational postauthorization safety study to describe the safety of ustekinumab and other Crohn's disease treatments in a cohort of patients with Crohn's disease Ongoing	To monitor the long-term safety profile of STELARA use in adult patients with moderately to severely active CD.	• Venous thromboembolism • Long-term safety in adult patients with moderately to severely active Crohn's disease	Protocol submission	27 September 2017
			Start of data collection	31 December 2019
			End of data collection	30 September 2022
			Final report	30 September 2023
Long-term extension of CNTO1275UCO3001 (A Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter protocol to evaluate the safety and efficacy of ustekinumab induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis) Ongoing	To evaluate the long-term safety of STELARA in adult patients with moderately to severely active UC from maintenance Week 44 through Week 220.	• Long-term safety in adult patients with moderately to severely active ulcerative colitis	Protocol submission	January 2019
			Trial start	19 August 2015 (start of induction phase of trial)
			Trial finish	31 December 2021
			Final report	31 December 2022

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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) Planned	To evaluate the long-term safety 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	To be determined
			End of data collection	31 August 2026
			Final report	31 March 2028
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) Planned	To evaluate the long-term safety 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	To be determined
			End of data collection	31 August 2026
			Final report	30 September 2027

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)

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 systemic hypersensitivity reactions	Routine risk communication: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.3 (Contraindications)* *SmPC section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet section 2* *SmPC section 4.8 (Undesirable Effects) and Package Leaflet section 4* Routine risk minimization activities recommending specific clinical measures to address the risk: *Treatment with STELARA is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients (SmPC section 4.3; Contraindications).* *If an anaphylactic or other serious hypersensitivity reaction occurs, appropriate therapy should be instituted and administration of STELARA should be discontinued (SmPC section 4.4; Special Warnings and Precautions for Use).* Other routine risk minimization measures beyond the Product Information: *Legal status: Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.*
Facial palsy	Routine risk communication: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.8 (Undesirable Effects) and Package Leaflet 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 by physicians experienced in the diagnosis and treatment of the applicable indication.*

Safety Concern	Routine Risk Minimization Activities
Pustular psoriasis	Routine risk communication: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.8 (Undesirable Effects) and Package Leaflet 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 by physicians experienced in the diagnosis and treatment of the applicable indication.*
Erythrodermic psoriasis	Routine risk communication: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet section 2* *SmPC section 4.8 (Undesirable Effects) and Package Leaflet section 4* Routine risk minimization activities recommending specific clinical measures to address the risk: *As part of the monitoring of the patient's psoriasis, physicians should be alert for symptoms of erythrodermic psoriasis or exfoliative dermatitis. If these symptoms occur, appropriate therapy should be instituted. STELARA should be discontinued if a drug reaction is suspected (SmPC section 4.4; Special Warnings and Precautions for Use).* Other routine risk minimization measures beyond the Product Information: *Legal status: Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.*

Safety Concern	Routine Risk Minimization Activities
Serious infections (including mycobacterial and salmonella infections)	Routine risk communication: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.3 (Contraindications)* *SmPC section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet section 2* *SmPC section 4.8 (Undesirable Effects) and Package Leaflet section 4* Routine risk minimization activities recommending specific clinical measures to address the risk: *Treatment with STELARA is contraindicated in patients with clinically important, active infections (SmPC Section 4.3; Contraindications) and should not be initiated until such an infection resolves. Prior to administering STELARA, patients should be evaluated for TB infection and treatment of latent TB should be initiated. Anti-TB therapy should also be considered in 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. If a patient develops a serious infection, the patient should discontinue STELARA until the infection resolves (SmPC section 4.4; Special Warnings and Precautions for Use).* Other routine risk minimization measures beyond the Product Information: *Legal status: Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.*
Malignancy	Routine risk communication: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet section 2* *SmPC section 4.8 (Undesirable Effects)* Routine risk minimization activities recommending specific clinical measures to address the risk: *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 non-melanoma skin cancer (SmPC section 4.4; Special Warnings and Precautions for Use).* Other routine risk minimization measures beyond the Product Information: *Legal status: Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.*

Safety Concern	Routine Risk Minimization Activities
Cardiovascular events	Routine risk communication: *SmPC section 4.2 (Posology and Method of Administration)* 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 by physicians experienced in the diagnosis and treatment of the applicable indication.*
Serious depression including suicidality	Routine risk communication: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.8 (Undesirable Effects) and Package Leaflet section 4* *Serious depression including suicidality is not specifically mentioned in the SmPC.* 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 by physicians experienced in the diagnosis and treatment of the applicable indication.*
Reversible posterior leukoencephalopathy syndrome	Routine risk communication: *SmPC section 4.2 (Posology and Method of Administration)* 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 by physicians experienced in the diagnosis and treatment of the applicable indication.*
Venous thromboembolism	Routine risk communication: *SmPC section 4.2 (Posology and Method of Administration)* 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 by physicians experienced in the diagnosis and treatment of the applicable indication.*

Safety Concern	Routine Risk Minimization Activities
Exposure during pregnancy	Routine risk communication: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.6 (Fertility, Pregnancy, and Lactation) and Package Leaflet section 2* Routine risk minimization activities recommending specific clinical measures to address the risk: *It is preferable to avoid the use of STELARA in pregnancy as a precautionary measure. Women of childbearing potential should use effective methods of contraception during treatment and for at least 15 weeks after treatment (SmPC section 4.6; Fertility, Pregnancy, and Lactation).* Other routine risk minimization measures beyond the Product Information: *Legal status: Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.*
Use in patients with a history of latent tuberculosis or tuberculosis	Routine risk communication: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet Section 2* Routine risk minimization activities recommending specific clinical measures to address the risk: *Prior to administering STELARA, patients should be evaluated for TB infection and treatment of latent TB should be initiated. Anti-TB therapy should also be considered in 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. If a patient develops a serious infection, the patient should discontinue STELARA until the infection resolves (SmPC section 4.4; Special Warnings and Precautions for Use).* Other routine risk minimization measures beyond the Product Information: *Legal status: Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.*
Use in patients with concurrent malignancy or a history of malignancy	Routine risk communication: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet section 2* 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 by physicians experienced in the diagnosis and treatment of the applicable indication.*

Safety Concern	Routine Risk Minimization Activities
Use in patients with recent or concomitant use of immunosuppressive therapy other than methotrexate, 6-mercaptopurine, azathioprine, 5-aminosalicylic acid, and corticosteroids	Routine risk communication: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet section 2* *SmPC section 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction)* 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 by physicians experienced in the diagnosis and treatment of the applicable indication.*
Long-term safety in pediatric psoriasis patients 6 years and older	Routine risk communication: *SmPC section 4.2 (Posology and Method of Administration)* 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 by physicians experienced in the diagnosis and treatment of the applicable indication.*
Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	Routine risk communication: *SmPC section 4.2 (Posology and Method of Administration)* 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 by physicians experienced in the diagnosis and treatment of the applicable indication.*
Long-term safety in adult patients with moderately to severely active Crohn's disease	Routine risk communication: *SmPC section 4.2 (Posology and Method of Administration)* 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 by physicians experienced in the diagnosis and treatment of the applicable indication.*

Safety Concern	Routine Risk Minimization Activities
Long-term safety in adult patients with moderately to severely active ulcerative colitis	Routine risk communication: *SmPC section 4.2 (Posology and Method of Administration)* 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 by physicians experienced in the diagnosis and treatment of the applicable indication.*

V.2. Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

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 systemic hypersensitivity reactions	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.3 (Contraindications)* *SmPC section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet section 2* *SmPC section 4.8 (Undesirable Effects) and Package Leaflet section 4* Additional risk minimization measures: *No additional risk minimization measures.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: *C0168Z03 PSOLAR* • *Final study report due date: 30 June 2022*

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Facial palsy	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.8 (Undesirable Effects) and Package Leaflet section 4* Additional risk minimization measures: *No additional risk minimization measures.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: *C0168Z03 PSOLAR* • *Final study report due date: 30 June 2022*
Pustular psoriasis	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.8 (Undesirable Effects) and Package Leaflet section 4* Additional risk minimization measures: *No additional risk minimization measures.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: *C0168Z03 PSOLAR* • *Final study report due date: 30 June 2022*
Erythrodermic psoriasis	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet section 2* *SmPC section 4.8 (Undesirable Effects) and Package Leaflet section 4* Additional risk minimization measures: *No additional risk minimization measures.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: *C0168Z03 PSOLAR* • *Final study report due date: 30 June 2022*

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serious infections (including mycobacterial and salmonella infections)	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.3 (Contraindications)* *SmPC section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet section 2* *SmPC section 4.8 (Undesirable Effects) and Package Leaflet section 4* Additional risk minimization measures: *No additional risk minimization measures.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: *C0168Z03 PSOLAR* • *Final study report due date: 30 June 2022* *STELARA UC/CD PASS using Swedish Registers* • *Final study report due date: 31 March 2028* *STELARA UC PASS using SNDS* • *Final study report due date: 30 September 2027*
Malignancy	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet section 2* *SmPC section 4.8 (Undesirable Effects)* Additional risk minimization measures: *No additional risk minimization measures.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: *C0168Z03 PSOLAR* • *Final study report due date: 30 June 2022* *STELARA UC/CD PASS using Swedish Registers* • *Final study report due date: 31 March 2028* *STELARA UC PASS using SNDS* • *Final study report due date: 30 September 2027*

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Cardiovascular events	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* Additional risk minimization measures: *No additional risk minimization measures.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: *C0168Z03 PSOLAR* • *Final study report due date: 30 June 2022* *STELARA UC/CD PASS using Swedish Registers (MACE only)* • *Final study report due date: 31 March 2028* *STELARA UC PASS using SNDS (MACE only)* • *Final study report due date: 30 September 2027*
Serious depression including suicidality	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.8 (Undesirable Effects) and Package Leaflet section 4* Additional risk minimization measures: *No additional risk minimization measures.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *C0168Z03 PSOLAR* • *Final study report due date: 30 June 2022*
Reversible posterior leukoencephalopathy syndrome	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* Additional risk minimization measures: *No additional risk minimization measures.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: *C0168Z03 PSOLAR* • *Final study report due date: 30 June 2022*

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Venous thromboembolism	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* Additional risk minimization measures: *No additional risk minimization measures.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: *RRA-20745* • *Final study report due date: 30 September 2023* *STELARA UC/CD PASS using Swedish Registers* • *Final study report due date: 31 March 2028* *STELARA UC PASS using SNDS* • *Final study report due date: 30 September 2027*
Exposure during pregnancy	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.6 (Fertility, Pregnancy, and Lactation) and Package Leaflet section 2* Additional risk minimization measures: *No additional risk minimization measures.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CNTO1275PSO4007 (Pregnancy Research Initiative)* • *Final study report due date: 01 December 2021*
Use in patients with a history of latent tuberculosis or tuberculosis	Routine risk minimization measures: *SmPC Section 4.2 (Posology and Method of Administration)* *SmPC Section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet Section 2* Additional risk minimization measures: *No additional risk minimization measures.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *C0168Z03 PSOLAR* • *Final study report due date: 30 June 2022*

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in patients with concurrent malignancy or a history of malignancy	Routine risk minimization measures: *SmPC Section 4.2 (Posology and Method of Administration)* *SmPC Section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet section 2* Additional risk minimization measures: *No additional risk minimization measures.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *C0168Z03 PSOLAR* • *Final study report due date: 30 June 2022*
Use in patients with recent or concomitant use of immunosuppressive therapy other than methotrexate, 6-mercaptopurine, azathioprine, 5-aminosalicylic acid, and corticosteroids	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet section 2* *SmPC section 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction)* Additional risk minimization measures: *No additional risk minimization measures.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *C0168Z03 PSOLAR* • *Final study report due date: 30 June 2022*
Long-term safety in pediatric psoriasis patients 6 years and older	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* Additional risk minimization measures: *No additional risk minimization measures.*	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*

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: *SmPC section 4.2 (Posology and Method of Administration)* Additional risk minimization measures: *No additional risk minimization measures.*	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: *SmPC section 4.2 (Posology and Method of Administration)* Additional risk minimization measures: *No additional risk minimization measures.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *RRA-20745* • *Final study report due date: 30 September 2023* *STELARA UC/CD PASS using Swedish Registers* • *Final study report due date: 31 March 2028*
Long-term safety in adult patients with moderately to severely active ulcerative colitis	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* Additional risk minimization measures: *No additional risk minimization measures.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: *Long-term extension of CNTO1275UCO3001* • *Final study report due date: 31 December 2022* *STELARA UC/CD PASS using Swedish Registers* • *Final study report due date: 31 March 2028* *STELARA UC PASS using SNDS* • *Final study report due date: 30 September 2027*

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 give essential information to healthcare professionals (HCPs) 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, Crohn's disease (CD), and ulcerative colitis (UC) (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 Package Leaflet and SmPC addressed to patients and HCPs;
- 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 (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of 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	Serious systemic hypersensitivity reactions Facial palsy Pustular psoriasis Erythrodermic psoriasis
Important potential risks	Serious infections (including mycobacterial and salmonella infections) Malignancy Cardiovascular events Serious depression including suicidality Reversible posterior leukoencephalopathy syndrome Venous thromboembolism Exposure during pregnancy
Missing information	Use in patients with a history of latent tuberculosis (TB) or TB Use in patients with concurrent malignancy or a history of malignancy Use in patients with recent or concomitant use of immunosuppressive therapy other than methotrexate (MTX), 6-mercaptopurine (6-MP), azathioprine (AZA), 5-aminosalicylic acid (5-ASA), and corticosteroids 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

II.B. Summary of Important Risks

Important identified risk: Serious systemic hypersensitivity reactions	
Evidence for linking the risk to the medicine	Serious systemic hypersensitivity reactions have been noted in the clinical trial program. Serious systemic hypersensitivity reactions related to ustekinumab have been reported in the postmarketing setting. Serious hypersensitivity reactions are considered an adverse drug reaction (ADR) for STELARA (SmPC section 4.8 [Undesirable Effects] and Package Leaflet section 4).
Risk factors and risk groups	In clinical trials for STELARA, there was no apparent association between a subject's antibody-to-ustekinumab status and hypersensitivity reactions. There are no known risk factors for the development of serious systemic hypersensitivity with ustekinumab.
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.3 (Contraindications)* *SmPC section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet section 2* *SmPC section 4.8 (Undesirable Effects) and Package Leaflet section 4* Additional risk minimization measures: *No additional risk minimization measures.*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *C0168Z03 PSOLAR* See section II.C of this summary for an overview of the postauthorization development plan.

Important identified risk: Facial palsy	
Evidence for linking the risk to the medicine	Facial palsy was reported in ustekinumab clinical trials across indications, as well as in the postmarketing setting as spontaneous reports in psoriasis patients. Due to the lack of data on facial palsy in psoriasis, the MAH performed an epidemiologic analysis and found that the incidence of facial palsy in ustekinumab clinical trials was similar to that in the general population in the US. Facial palsy is included as an ADR for STELARA (SmPC section 4.8 [Undesirable Effects] and Package Leaflet section 4).
Risk factors and risk groups	There is no race, geographic, or sex predilection for facial palsy. It can be seen in patients of any age but increases over the age of 65 years and decreases under the age of 13 years. The risk of Bell's palsy is 3 times greater during pregnancy, especially in the third trimester or in the first postpartum week. Diabetes, hypertension, and hyperlipidemia have all been associated with Bell's palsy in the literature. A positive family history is elicited in 8% of patients. In a Finnish study, the 2 most common causes of facial palsy in children were Borrelia burgdorferi (30%) and varicella zoster virus (11%). It is common for patients with facial palsy to have had a history of a recent viral illness.
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.8 (Undesirable Effects) and Package Leaflet section 4* Additional risk minimization measures: *No additional risk minimization measures.*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *C0168Z03 PSOLAR* See section II.C of this summary for an overview of the postauthorization development plan.

Important identified risk: Pustular psoriasis	
Evidence for linking the risk to the medicine	Pustular psoriasis has been reported in ustekinumab clinical trials and in the postmarketing setting. Some of the postmarketing reports suggest a causal relationship with STELARA based on temporal relationship, recurrence with re challenge, and presence of the rare palmoplantar pattern. Pustular psoriasis is considered an ADR for STELARA (SmPC section 4.8 [Undesirable Effects] and Package Leaflet section 4).
Risk factors and risk groups	Pustular psoriasis can occur de novo or may be triggered in certain settings. Factors that could trigger pustular psoriasis include internal medications, irritating topical agents, overexposure to UV light, pregnancy, systemic steroids, infections, emotional stress, and sudden withdrawal of systemic medications or potent topical steroids. There have been case reports of pustular psoriasis in CD patients exposed to anti TNF treatment.
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.8 (Undesirable Effects) and Package Leaflet section 4* Additional risk minimization measures: *No additional risk minimization measures.*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *C0168Z03 PSOLAR* See section II.C of this summary for an overview of the postauthorization development plan.

Important identified risk: Erythrodermic psoriasis	
Evidence for linking the risk to the medicine	The clinical data in psoriasis and PsA showed no imbalance in ustekinumab-treated patients compared with placebo, no evidence of a dose response, and very few adverse events (AEs) overall. Postmarketing reports of new-onset erythrodermic psoriasis have been received; most cases included confounding elements (eg, a triggering element was noted, the diagnosis was in question, or ustekinumab was continued with resolution). Literature evidence is inconclusive since some support the use of ustekinumab in patients with erythrodermic psoriasis, while others reported AEs of erythrodermic psoriasis and exfoliative dermatitis after the use of ustekinumab. Therefore, based on postmarketing reports of erythrodermic psoriasis, it was included as an ADR for STELARA (SmPC section 4.8 [Undesirable Effects] and Package Leaflet section 4).
Risk factors and risk groups	Abrupt withdrawal of systemic or potent topical steroids; unstable psoriasis; trauma; infections; drugs such as lithium, anti-malarial medications, trimethoprim, and sulfamethoxazole; withdrawal of systemic glucocorticoid or other immunomodulating agents; and environmental, psychological, and metabolic factors can trigger psoriasis and the erythrodermic form of the disease. There have been case reports of pustular psoriasis in CD patients exposed to anti-TNF. Erythrodermic psoriasis has been noted to appear often in people who have unstable plaque psoriasis.
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet section 2* *SmPC section 4.8 (Undesirable Effects) and Package Leaflet section 4* Additional risk minimization measures: *No additional risk minimization measures.*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *C0168Z03 PSOLAR* See section II.C of this summary for an overview of the postauthorization development plan.

Important potential risk: Serious infections (including mycobacterial and salmonella infections)	
Evidence for linking the risk to the medicine	Published nonclinical and medical literature suggest that inhibition of IL-12/23 may predispose patients to serious infections. 'Serious infection (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-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: 1.0-4.5) and age >50 years (OR=26.5; 95% CI: 10.9-67.3). Similarly, in a 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. 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

Important potential risk: Serious infections (including mycobacterial and salmonella infections)	
	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 section 4.2 (Posology and Method of Administration)* *SmPC section 4.3 (Contraindications)* *SmPC section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet section 2* *SmPC section 4.8 (Undesirable Effects) and Package Leaflet section 4* Additional risk minimization measures: *No additional risk minimization measures.*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *C0168Z03 PSOLAR* *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. Since 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 2 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 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 PUVA and immunosuppressants, including cyclosporin and possibly 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 section 4.2 (Posology and Method of Administration)* *SmPC section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet section 2* *SmPC section 4.8 (Undesirable Effects)* Additional risk minimization measures: *No additional risk minimization measures.*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *C0168Z03 PSOLAR* *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 event (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 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 2 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	The risk factors in the development of CV disease are well known and include hypertension, hypercholesterolemia, diabetes, smoking, age, male sex, obesity, and family history. The PsA and the psoriasis populations share certain risk factors such as increased CV risk, increased body weight, and increased BMI, which have also been observed in CD patients.
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* Additional risk minimization measures: *No additional risk minimization measures.*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *C0168Z03 PSOLAR* *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 Package Leaflet 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 4.2 (Posology and Method of Administration)* *SmPC section 4.8 (Undesirable Effects) and Package Leaflet section 4* Additional risk minimization measures: *No additional risk minimization measures.*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *C0168Z03 PSOLAR* See section II.C of this summary for an overview of the postauthorization development plan.

Important potential risk: Reversible posterior leukoencephalopathy syndrome	
Evidence for linking the risk to the medicine	Two cases of reversible posterior leukoencephalopathy syndrome (RPLS) were reported in clinical trials, only 1 of which was in an approved indication (psoriasis). Events of RPLS have been reported in the postmarketing setting, including individual reports in the literature, but there is no evidence for causal association or mechanistic or scientific evidence for causality.
Risk factors and risk groups	Reversible posterior leukoencephalopathy syndrome has been associated with diverse clinical scenarios including hypertensive encephalopathy, pre-eclampsia, renal failure, electrolyte abnormalities, rheumatologic diseases (including SLE), and cytotoxic and immunosuppressant drugs. Case reports in the literature have cited possible association with multiple drugs including cyclosporin, MTX, tacrolimus (Prograf), rituximab (Rituxan), bevacizumab (Avastin), bortezomib (Velcade), and some TNF blockers.
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* Additional risk minimization measures: *No additional risk minimization measures.*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *C0168Z03 PSOLAR* See section II.C of this summary for an overview of the postauthorization development plan.

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 2 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 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 trials through Week 96, and from 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 UK reported that there was increased risk of VTE during disease flares and chronic activity. In a Danish population study that included children and adults, and 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. Risk has also been reported to be greater for males, with an incidence rate of 1.34/1000 PY, than for females with an 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 1.14-10.5) and 2.97 (95% CI: 0.99-8.92), respectively.
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* Additional risk minimization measures: *No additional risk minimization measures.*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *RRA-20745* *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: Exposure during pregnancy	
Evidence for linking the risk to the medicine	The effects of ustekinumab during pregnancy are not known. Toxicokinetic analyses have confirmed that ustekinumab can cross the placenta; however, nonclinical studies have shown no effect. Cumulative safety data do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition, or postnatal development (SmPC section 4.6 [Fertility, pregnancy and lactation]), but cases of exposure during pregnancy are limited. 'Exposure during pregnancy' is considered an important potential risk because of the limitations of nonclinical investigations on this topic and the limited data in humans related to exposure during pregnancy.
Risk factors and risk groups	Patients who do not follow guidance on use of contraception or use contraception incorrectly are at risk for pregnancy. Most of the systemic antipsoriatic therapies are associated with significant toxic effects to the fetus and are recommended to be avoided during pregnancy. A recent update on the safety of IBD medications in pregnancy summarized that the available data provide reassuring information for providers caring for women with IBD and of childbearing age, although long-term effects of IBD medications on offspring need to be examined.
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.6 (Fertility, Pregnancy, and Lactation) and Package Leaflet section 2* Additional risk minimization measures: *No additional risk minimization measures.*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *CNTO1275PSO4007 (Pregnancy Research Initiative)* See section II.C of this summary for an overview of the postauthorization development plan.

Missing information: Use in patients with a history of latent tuberculosis or tuberculosis	
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet section 2* Additional risk minimization measures: *No additional risk minimization measures.*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *C0168Z03 PSOLAR* See section II.C of this summary for an overview of the postauthorization development plan.

Missing information: Use in patients with concurrent malignancy or a history of malignancy	
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet section 2* Additional risk minimization measures: *No additional risk minimization measures.*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *C0168Z03 PSOLAR* See section II.C of this summary for an overview of the postauthorization development plan.

Missing information: Use in patients with recent or concomitant use of immunosuppressive therapy other than methotrexate, 6-mercaptopurine, azathioprine, 5-aminosalicylic acid, and corticosteroids	
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet section 2* *SmPC section 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction)* Additional risk minimization measures: *No additional risk minimization measures.*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *C0168Z03 PSOLAR* 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	
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* Additional risk minimization measures: *No additional risk minimization measures.*
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	
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* Additional risk minimization measures: *No additional risk minimization measures.*
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	
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* Additional risk minimization measures: *No additional risk minimization measures.*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *RRA-20745* *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	
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.2 (Posology and Method of Administration)* Additional risk minimization measures: *No additional risk minimization measures*.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Long-term extension of CNTO1275UCO3001* *STELARA UC/CD PASS using Swedish Registers* *STELARA UC PASS using SNDS* See section II.C of this summary for an overview of the post-authorization development plan.

II.C. Postauthorization Development Plan

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

There are no studies that are conditions of the marketing authorization or specific obligations of STELARA.

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

Trial	Purpose of Trial
C0168Z03 (PSOLAR)	Objective: to evaluate the safety of STELARA in patients with moderate to severe plaque psoriasis (plaque psoriasis [overlapping forms of psoriasis may be included]). To address the safety concerns of: • Serious systemic hypersensitivity reactions • Facial palsy • Pustular psoriasis • Erythrodermic psoriasis • Serious infections (including mycobacterial and salmonella infections) • Malignancy • Cardiovascular events • Serious depression including suicidality • Reversible posterior leukoencephalopathy syndrome • Use in patients with a history of latent tuberculosis or tuberculosis • Use in patients with concurrent malignancy or a history of malignancy • Use in patients with recent or concomitant use of immunosuppressive therapy other than methotrexate, 6-mercaptopurine, azathioprine, 5-aminosalicylic acid, and corticosteroids.
CNTO1275PSO4007 (Pregnancy Research Initiative)	Objective: the collection and analysis of information pertaining to pregnancy outcomes of women exposed to STELARA during pregnancy and health status in the first year of life of infants born to women following prenatal exposure to STELARA compared with controls. To address the safety concern of 'Exposure during pregnancy.'
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.

Trial	Purpose of Trial
RRA-20745	Objective: to monitor the long-term safety profile of STELARA use in adult patients with moderately to severely active CD To address the safety concerns of: • Long-term safety in adult patients with moderately to severely active Crohn's disease • Venous thromboembolism.
Long-term extension of CNTO1275UCO3001	Objective: to evaluate the long-term safety of STELARA in adult patients with moderately to severely active UC from maintenance Week 44 through Week 220. To address the safety concern of 'Long-term safety in adult patients with moderately to severely active ulcerative colitis.'
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
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

PART VII: ANNEXES

Table of Contents

Annex 1	EudraVigilance Interface
Annex 2	Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program
Annex 3	Protocols for Proposed, On-going, and Completed Studies in the Pharmacovigilance Plan
	Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP
	Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP
	Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority
Annex 4	Specific Adverse Drug Reaction Follow-up Forms
Annex 5	Protocols for Proposed and On-going Studies in RMP Part IV
Annex 6	Details of Proposed Additional Risk Minimization Measures (if applicable)
Annex 7	Other Supporting Data (including referenced material)
Annex 8	Summary of Changes to the Risk Management Plan Over Time

Annex 1: Eudravigilance Interface

(electronic only)

Annex 2: Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Table 1 Annex II: Planned and Ongoing Studies

Study	Summary of Objectives	Safety Concerns Addressed	Protocol Reference Milestones
C0168Z03 PSOLAR (plaque psoriasis [overlapping forms of psoriasis may be included]): A multicenter, prospective, observational registry of patients with psoriasis who are candidates for systemic therapy including biologics Category 3	To evaluate the safety of STELARA in patients with moderate to severe plaque psoriasis (plaque psoriasis [overlapping forms of psoriasis may be included]).	• Serious systemic hypersensitivity reactions • Facial palsy • Pustular psoriasis • Erythrodermic psoriasis • Serious infections (including mycobacterial and salmonella infections) • Malignancy • Cardiovascular events • Serious depression including suicidality • Reversible posterior leukoencephalopathy syndrome • Use in patients with a history of latent tuberculosis or tuberculosis • Use in patients with concurrent malignancy or a history of malignancy • Use in patients with recent or concomitant use of immunosuppressive therapy other than methotrexate, 6-mercaptopurine, azathioprine, 5-aminosalicylic acid, and corticosteroids	Mod5.3.6/Protocol C0168Z03 1. Protocol submission: 25 June 2009 2. Registry start: 20 June 2007: The registry was expanded to include STELARA patients on 19 March 2009 and the first STELARA patient was enrolled in PSOLAR on 24 March 2009. 3. Registry finish: 06 September 2021 4. Final report: 30 June 2022

Study	Summary of Objectives	Safety Concerns Addressed	Protocol Reference Milestones
CNTO1275PSO4007 (Pregnancy Research Initiative): Exposure to ustekinumab during pregnancy: A review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers Category 3	Collection and analysis of information pertaining to pregnancy outcomes of women exposed to STELARA during pregnancy and health status in the first year of life of infants born to women following prenatal exposure to STELARA compared with controls	• Exposure during pregnancy	Seq0252/Mod5.3.6/Registry Study Protocol CNTO1275PSO4007-Am3 1. Protocol submission: 25 June 2009 2. Registry start: 20 July 2009 3. Registry finish: 15 December 2020 4. Final report: 01 December 2021
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 Category 3	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	Mod5.3.6/Adolescent PASS Protocol 1. Protocol submission: 21 December 2015 2. Registry start: 25 October 2017 3. Registry finish: 31 August 2032 4. Final report: 31 March 2033

Study	Summary of Objectives	Safety Concerns Addressed	Protocol Reference Milestones
RRA-20745: An observational postauthorization safety study to describe the safety of ustekinumab and other Crohn's disease treatments in a cohort of patients with Crohn's disease Category 3	To monitor the long-term safety profile of STELARA use in adult patients with moderately to severely active CD	• Venous thromboembolism • Long-term safety in adult patients with moderately to severely active Crohn's disease	Seq0230/Mod1.8.2/Updated draft protocol - Crohn's Disease Registry 1. Protocol submission: 27 September 2017 2. Start of data collection: 31 December 2019 3. End of data collection: 30 September 2022 4. Final report: 30 September 2023
Long-term extension of CNTO1275UCO3001 (A Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter protocol to evaluate the safety and efficacy of ustekinumab induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis) Category 3	To evaluate the long-term safety of ustekinumab in adult patients with moderately to severely active UC from maintenance Week 44 through Week 220.	• Long-term safety in adult patients with moderately to severely active ulcerative colitis	Mod5.3.5.1/CNTO1275UCO 3001 Protocol 1. Protocol submission: January 2019 2. Trial start: 19 August 2015 (start of induction phase of trial) 3. Trial finish: 31 December 2021 4. Final report: 31 December 2022

Study	Summary of Objectives	Safety Concerns Addressed	Protocol Reference Milestones
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) Category 3	To evaluate the long-term safety 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	Mod1.8.2/Ulcerative Colitis and Crohn's disease PASS Protocol (SWIBREG-UST) 1. Protocol submission: 23 June 2020 2. Start of data collection: To be determined 3. End of data collection: 31 August 2026 4. Final report: 31 March 2028
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) Category 3	To evaluate the long-term safety 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	Mod1.8.2/Ulcerative Colitis PASS Protocol (SNDS-UST) 1. Protocol submission: 23 June 2020 2. Start of data collection: To be determined 3. End of data collection: 31 August 2026 4. Final report: 30 September 2027

Table 2 Annex II: Completed Studies

Study	Summary of Objectives	Safety Concerns Addressed	Date of Final Study Report Submission Cross-reference to Report
Long-term extension of CNTO1275CRD3003 (A Phase 3, randomized, double blind, placebo-controlled, parallel-group, multicenter trial to evaluate the safety and efficacy of ustekinumab maintenance therapy in adult patients with moderately to severely active Crohn's disease) Category 3	To evaluate the long-term safety of ustekinumab in adult patients with moderately to severely active CD from Week 44 through Week 272	• Venous thromboembolism • Long-term safety in adult patients with moderately to severely active Crohn's disease	31 July 2020 Mod5.3.5.1/CNTO1275CRD3003 Clinical Study Report - Week 272
CNTO1275PSO4005 (Nordic Database Initiative): A review and analysis of AEs from the Swedish and Danish national registry systems Category 3	Collection and analysis of AEs/SAEs of interest in psoriasis patients (any form of psoriasis) exposed to STELARA, relative to the background risk in non-biologic-exposed controls	• Serious systemic hypersensitivity reactions • Facial palsy • Serious infections (including mycobacterial and salmonella infections) • Malignancy • Cardiovascular events • Serious depression including suicidality • Reversible posterior leukoencephalopathy syndrome • Use in patients with a history of latent tuberculosis or tuberculosis • Use in patients with concurrent malignancy or a history of malignancy	01 September 2020 Mod5.3.6/Final Safety Registry Report - CNTO1275PSO4005

Annex 3: Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan

Table of Contents

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority

Protocols presented below fulfill the requirements of Part A, B, and C and are presented by approved protocols and final protocols not reviewed or not approved.

Approved protocols:

Trial	Name of Procedure	Date of Procedure outcome	Reference to full protocol
C0168Z03 PSOLAR (plaque psoriasis [overlapping forms of psoriasis may be included]): A multicenter, prospective, observational registry of patients with psoriasis who are candidates for systemic therapy including biologics	MEA 22.10	13 October 2016	Mod5.3.6/Protocol C0168Z03
CNTO1275PSO4005 (Nordic Database Initiative): A review and analysis of AEs from the Swedish and Danish national registry systems	FUM 23.6	23 July 2015	Seq0175/Mod5.3.6/Registry Study Protocol CNTO1275PSO4005 - Am2
CNTO1275PSO4007 (Pregnancy Research Initiative): Exposure to ustekinumab during pregnancy: A review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers	MEA 24.9	23 February 2017	Seq0252/Mod5.3.6/Registry Study Protocol CNTO1275PSO4007-Am3

Trial	Name of Procedure	Date of Procedure outcome	Reference to full protocol
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	MEA 44.2	23 February 2017	Mod5.3.6/Adolescent PASS Protocol
Long-term extension of CNTO1275CRD3003 (A Phase 3, randomized, double blind, placebo controlled, parallel-group, multicenter trial to evaluate the safety and efficacy of ustekinumab maintenance therapy in adult patients with moderately to severely active Crohn's disease)	X/0049/G	11 November 2016	Mod5.3.5.1/CNTO1275CRD3003 Protocol
Long-term extension of CNTO1275UCO3001 (A Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter protocol to evaluate the safety and efficacy of ustekinumab induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis)	II/0071	03 September 2019	Mod5.3.5.1/CNTO1275UCO3001 Protocol

Final protocols not reviewed or not approved:

Not applicable.

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Table of Contents

Adverse Reaction Follow-up Questionnaire for Hypersensitivity

Adverse Reaction Follow-up Questionnaire for Facial Palsy (Bell's Palsy)

Adverse Reaction Follow-up Questionnaire for Psoriasis variant (Pustular, Erythrodermic, Guttate)

Adverse Reaction Follow-up Questionnaire for Serious Infections and Opportunistic Infections

Adverse Reaction Follow-up Questionnaire for Tuberculosis

Adverse Reaction Follow-up Questionnaire for Malignancies

Adverse Reaction Follow-up Questionnaire for Lymphoma

Adverse Reaction Follow-up Questionnaire for Cardiovascular Events

Adverse Reaction Follow-up Questionnaire for Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Adverse Reaction Follow-up Questionnaire for Venous Thromboembolism (VTE)

Follow-up Forms

ustekinumab (STELARA®) Targeted Follow-up Questionnaire for Hypersensitivity

Manufacturer Control Number Date of Report [dd-MMM-yyyy]

Person providing this information:			
Name:			
Address:			
City:		State:	ZIP/Postal Code:
Country:		Telephone:	Fax:
Relationship to patient:	☐ Physician	☐ Nurse	☐ Pharmacist
	☐ Other health care professional (please explain)		
	☐ Other (please explain)		
Signature:		Date: [dd-MMM-yyyy]	

Note to LSOs: The following statement may be removed or modified in accordance with local requirements.
For reports originating from the United States: The Health Insurance Portability and Accountability Act (HIPAA) specifically permits covered entities (such as pharmacists, physicians or hospitals) to report adverse events and other information related to the quality, effectiveness and safety of FDA regulated products both to the manufacturers and directly to the FDA.

1. Patient Demographics

Note: If regarding a clinical trial subject, please provide ONLY the demographics under 1a, before completing the rest of the questionnaire.

a. Clinical Trials Only
Patient DOB: [dd-MMM-yyyy] Subject ID Number:
Site ID Number: Protocol Number:

b. Non-Clinical Trials
Patient name:
Patient DOB: [dd-MMM-yyyy] Patient gender: ☐ M ☐ F
Patient's country of origin: Patient height Patient weight lbs kg
Patient's ethnicity: ☐ White ☐ Hispanic ☐ Black ☐ Asian/Pacific Islander
☐ Native American ☐ Unknown

2. ustekinumab (STELARA®) details

Indication for use ☐ Psoriasis ☐ Other (specify)
Dose ☐ 45 mg ☐ 90 mg
Dosing Interval ☐ Every 12 weeks ☐ Other (specify)
Start date [dd-MMM-yyyy] End date [dd-MMM-yyyy]
Number of injections given prior to hypersensitivity reaction
Date of Last **ustekinumab (STELARA®)** injection given prior to hypersensitivity reaction [dd-MMM-yyyy]
Date of hypersensitivity reaction [dd-MMM-yyyy]

MCN:

3. Concomitant Medications *(attach additional pages as needed)*

Medication	Dose/Route of Administration	Start Date / Stop Date [dd-MMM-yyyy]

4. List relevant medical history *(include drug allergies, other know allergies, etc. below)*

5. Were any new medications (prescribed or OTC) received by the patient prior to the hypersensitivity reactions?

☐ Yes (if yes, list additional details below) ☐ No

6. Diagnosis

Time from injection to onset of symptoms ☐ minutes, ☐ hours, ☐ days

Patient's symptoms (check all that apply)

☐ Urticaria ☐ Substernal chest pains ☐ Rash ☐ Fever
☐ Arthralgia ☐ Dyspnea ☐ Facial edema ☐ Laryngeal edema
☐ Myalgia ☐ Bronchospasm / Wheezing

7. Premedication – Was the patient pre-medicated prior to the injection?

☐ **No** ☐ **Yes** (If yes, list pre-medication regiment below)

Medication	Dose/Route of Administration	Start Date / Stop Date [dd-MMM-yyyy]

8. Treatment and Response *(List patient treatment regiment and outcome of event below. Include dates of treatment, response to treatment, and hospitalization dates if relevant)*

How was the patient treated (specify medications, treatment regiment and additional details below?)

☐ Antihistamines ☐ NSAIDS ☐ Narcotic analgesia ☐ Steroids
☐ Epinephrine ☐ Oxygen ☐ Other (specify details below)

Duration of the event ☐ minutes, ☐ hours, ☐ days (check one)

Did the event resolve? ☐ Yes ☐ No (list additional details below)

Was **ustekinumab (STELARA®)** re-administered after the event?

☐ Yes (if yes, list additional details below) ☐ No

Was the patient pre-medicated prior to the next injection?

☐ Yes (If yes, list pre-medication regimen below) ☐ No

Did event recur or worsen? ☐ Yes (if yes, list additional details below) ☐ No

9. Comments:

ustekinumab (STELARA®) Targeted Follow-up Questionnaire (TFUQ) for Facial Palsy (Bell's Palsy)

Manufacturer Control Number Date of Report [dd-MMM-yyyy]

Person providing this information:			
Name:			
Address:			
City:		State:	ZIP/Postal Code:
Country:		Telephone:	Fax:
Relationship to patient:	☐ Physician	☐ Nurse	☐ Pharmacist
	☐ Other health care professional (please explain)		
	☐ Other (please explain)		
Signature:		Date:	[dd-MMM-yyyy]

Note to LSOs: The following statement may be removed or modified in accordance with local requirements.
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1. Patient Demographics

Note: If regarding a clinical trial subject, please provide ONLY the demographics under 1a, before completing the rest of the questionnaire.

a. Clinical Trials Only
Patient DOB: [dd-MMM-yyyy] Subject ID Number:
Site ID Number: Protocol Number:

b. Non-Clinical Trials
Patient name:
Patient DOB: [dd-MMM-yyyy] Patient gender: ☐ M ☐ F
Patient's country of origin: Patient height Patient weight lbs kg
Patient's ethnicity: ☐ White ☐ Hispanic ☐ Black ☐ Asian/Pacific Islander
☐ Native American ☐ Unknown

2. ustekinumab (STELARA®) details

Indication for use ☐ Psoriasis ☐ Other (specify)
Dose ☐ 45 mg ☐ 90 mg Dosing Interval ☐ Every 12 weeks
☐ Other (specify)
Start date [dd-MMM-yyyy] End date [dd-MMM-yyyy]
Approximate total numbers of injections patient received

MCN:

3. Concomitant medications *(attach additional pages as needed)*

Medication	Dose/Route of Administration	Start Date / Stop Date [dd-MMM-yyyy]

4. List relevant medical history *(provide prior diagnoses and details of any checked items below)*

- ☐ Previous facial palsy (side, date if known)
- ☐ Recent infection of head/neck or systemic (e.g. Herpes simplex virus. Herpes zoster or Lyme disease)
- ☐ Previous neurologic disorder or neurodegenerative conditions
- ☐ Diabetes
- ☐ Recent pregnancy
- ☐ Previous administration of immunosuppressant medications (drug indication, duration)

5. Diagnosis *(List symptoms and signs, including side affected, and associated symptoms (such as hearing disturbance, rash, swallowing difficulty or slurred speech), hemi paresis, specific diagnosis, presence of any complicating factors, or coincident infections or illnesses, and results of any consultations.*

Date of first symptoms [dd-MMM-yyyy] Date of diagnosis [dd-MMM-yyyy]

6. Laboratory and radiology data *(List all relevant laboratory data below. Attach additional pages if needed.)*

Laboratory Test	**Date** [dd-MMM-yyyy]	**Results**

7. Treatment and response *(List any treatments provided such as antivirals or steroids and outcome of event below.)*

Did the event resolve? ☐ Yes ☐ No

If yes, list date that event was considered resolved [dd-MMM-yyyy]

Was **ustekinumab (STELARA®)** discontinued or temporarily interrupted due to the event?

☐ Yes ☐ No

Was **ustekinumab (STELARA®)** re-administered after the event? ☐ Yes ☐ No

If yes, did event recur or worsen (List details below)?

MCN:

8. **Were other causes of facial palsy excluded** *(e.g. Lyme disease, sarcoidosis*)

9. **Comments, please include any atypical features of presentation or course of facial palsy**

ustekinumab (STELARA®)Targeted Follow-up Questionnaire (TFUQ) for Psoriasis variant (Pustular, Erythrodermic, Guttate)

Manufacturer Control Number: Date of Report [dd-MMM-yyyy]

Person providing this information:			
Name:			
Address:			
City:		State:	ZIP/Postal Code:
Country:		Telephone:	Fax:
Relationship to patient:	☐ Physician	☐ Nurse	☐ Pharmacist
	☐ Other health care professional (please explain)		
	☐ Other (please explain)		
Signature:		Date: [dd-MMM-yyyy]	

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1. Patient Demographics

Note: If regarding a clinical trial subject, please provide ONLY the demographics under 1a, before completing the rest of the questionnaire.

a. Clinical Trials Only
Patient DOB: [dd-MMM-yyyy] Subject ID Number:
Site ID Number: Protocol Number:

b. Non-Clinical Trials
Patient name:
Patient DOB: [dd-MMM-yyyy] Patient gender: ☐ M ☐ F
Patient's country of origin: Patient height Patient weight lbs kg
Patient's ethnicity: ☐ White ☐ Hispanic ☐ Black ☐ Asian/Pacific Islander
☐ Native American ☐ Unknown

2. ustekinumab (Stelara®) Details

Indication for Use :
Dose at time of event (mg): Patient weight: _lbs _kg
Start Date: [dd-MMM-yyyy] End date [dd-MMM-yyyy]
Recent dose change? (Elaborate on timing/amount of dose change):

MCN:

3. Adverse Event

What is the adverse psoriatic event?

Time from initiation of **STELARA** to event:

a. Time from first dose:
b. Time from recent dose:

History of Psoriasis:

a. Type (Plaque, guttate, erythrodermic, pustular, etc.):
b. Duration (months or years):
c. Transition from one type of psoriasis to another: ☐ Y ☐ N
   If yes, please provide details (type changed from – to, triggering factor that may have contributes, duration, etc.):

4. Treatment and Outcome

Treatment was discontinued following event? ☐ Y ☐ N
Patient had an emergency department visit and was discharged? ☐ Y ☐ N
Patient was hospitalized ☐ Y ☐ N
Patient died? ☐ Y ☐ N (If yes, elaborate on cause of death)
Associated, or any preceding relevant, treatment emergent adverse events

Concomitant medications– *Attach additional pages as needed.*

Medication	Dose/route of administration	Start Date/Stop Date [dd-MMM-yyyy]

5. Medical History and Concurrent Conditions

Does this patient have a history of:

☐ History of dry skin
☐ History of stress (physiologic or psychological)
☐ History of skin injury
☐ History of streptococcal infection
☐ History of systemic infection (if yes, please provide details):
☐ Currently pregnant (if applicable)
☐ Smoking: previous history (number of pack years)
☐ History of excessive alcohol use ☐ History of sun burn
☐ Occupational/Exposure history (eg. Recent topical irritants)

Previous administration of medications (e.g. Lithium salts, Beta blockers, Steroids, Anti-malarials, sulfonamides, etc.)

MCN:

6. **Laboratory Evaluation** *(Please indicate the date performed)*:
   - ☐ PASI score
   - ☐ Skin biopsy

7. **Other Pertinent Information** *(e.g. Family history of type of psoriasis, HIV, RA, SLE, Celiac disease, or inherited immune deficiency disease):*

8. **Comments:**

ustekinumab (STELARA®) Targeted Follow-up Questionnaire (TFUQ) for Serious Infections and Opportunistic Infections

Manufacturer Control Number Date of Report [dd-MMM-yyyy]

Person providing this information:			
Name:			
Address:			
City:		State:	ZIP/Postal Code:
Country:		Telephone:	Fax:
Relationship to patient:	☐ Physician	☐ Nurse	☐ Pharmacist
	☐ Other health care professional (please explain)		
	☐ Other (please explain)		
Signature:		Date:	[dd-MMM-yyyy]

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1. Patient Demographics

Note: If regarding a clinical trial subject, please provide ONLY the demographics under 1a, before completing the rest of the questionnaire.

a. Clinical Trials Only
Patient DOB: [dd-MMM-yyyy] Subject ID Number:
Site ID Number: Protocol Number:

b. Non-Clinical Trials
Patient name:
Patient DOB: [dd-MMM-yyyy] Patient gender: ☐ M ☐ F
Patient's country of origin: Patient height Patient weight lbs kg
Patient's ethnicity: ☐ White ☐ Hispanic ☐ Black ☐ Asian/Pacific Islander
☐ Native American ☐ Unknown

2. Ustekinumab (STELARA®) details

Indication for use ☐ Psoriasis ☐ Other (specify)
Dose ☐ 45 mg ☐ 90 mg Dosing Interval ☐ Every 12 weeks
☐ Other (specify)
Start date [dd-MMM-yyyy] End date [dd-MMM-yyyy]
Approximate total numbers of injections patient received

MCN:

3. **Concomitant medications** *(attach additional pages as needed)*

Medication	Dose/Route of Administration	Start Date / Stop Date [dd-MMM-yyyy]

4. **List relevant medical history**

5. **Is the patient considered immunocompromised? If so, please provide details** *(underlying diagnoses, immunosuppressive therapy, etc.)*

6. **Diagnosis** *(list symptoms and signs, specific diagnosis and how event was diagnosed)*

Date of first symptoms: [dd-MMM-yyyy]
Date of diagnosis: [dd-MMM-yyyy]

7. **Laboratory and radiology data** *(List all relevant laboratory data below. Include culture results if available. Attach additional pages if needed)*

Laboratory Test	Date [dd-MMM-yyyy]	Results

8. **Treatment and response** *(List patient treatment regimen and outcome of event below. Include dates of treatment, response to treatment, and hospitalization dates if relevant)*

Did the event resolve? ☐ **Yes** ☐ **No**

If yes, list date that event was considered resolved: [dd-MMM-yyyy]
Was **ustekinumab (STELARA®)** discontinued or temporarily interrupted due to the event?
☐ Yes ☐ No
Was **ustekinumab (STELARA®)** re-administered after the event?
☐ Yes ☐ No
If yes, did event recur or worsen (List details below)?

9. **Were there any unusual features of the patient's presentation or clinical course?**

ustekinumab (STELARA®) Targeted Follow-up Questionnaire (TFUQ) for Tuberculosis

Manufacturer Control Number Date of Report [dd-MMM-yyyy]

Person providing this information:			
Name:			
Address:			
City:		State:	ZIP/Postal Code:
Country:		Telephone:	Fax:
Relationship to patient:	☐ Physician	☐ Nurse	☐ Pharmacist
	☐ Other health care professional (please explain)		
	☐ Other (please explain)		
Signature:		Date:	[dd-MMM-yyyy]

Note to LSOs: The following statement may be removed or modified in accordance with local requirements.
For reports originating from the United States: The Health Insurance Portability and Accountability Act (HIPAA) specifically permits covered entities (such as pharmacists, physicians or hospitals) to report adverse events and other information related to the quality, effectiveness and safety of FDA regulated products both to the manufacturers and directly to the FDA.

1. Patient Demographics

Note: If regarding a clinical trial subject, please provide ONLY the demographics under 1a, before completing the rest of the questionnaire.

a. Clinical Trials Only
Patient DOB: [dd-MMM-yyyy] Subject ID Number:
Site ID Number: Protocol Number:

b. Non-Clinical Trials
Patient name:
Patient DOB: [dd-MMM-yyyy] Patient gender: ☐ M ☐ F
Patient's country of origin: Patient height Patient weight lbs kg
Patient's ethnicity: ☐ White ☐ Hispanic ☐ Black ☐ Asian/Pacific Islander
☐ Native American ☐ Unknown

2. ustekinumab (STELARA®) details

Indication for use ☐ Psoriasis ☐ Other (specify)
Dose ☐ 45 mg ☐ 90 mg Dosing Interval ☐ Every 12 weeks
☐ Other (specify)
Start date [dd-MMM-yyyy] End date [dd-MMM-yyyy]
Approximate total numbers of injections patient received

MCN:

3. Concomitant medications (attach additional pages as needed)

Medication	Dose/Route of Administration	Start Date / Stop Date [dd-MMM-yyyy]

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

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

5. Laboratory and radiology data

a) PPD Testing

Was PPD testing performed ☐Yes ☐No **(go to section b)**
Which skin test was used? ☐ Intradermal ☐ Multipuncture
How many units were administered?
PPD Result; mm of in duration (0, if no duration)
Date of PPD: [dd-MMM-yyyy]
2nd PPD results (if applicable): mm of in duration
Date of second PPD: [dd-MMM-yyyy]

If either test was negative, were there any factors that may account for false negative (e.g. time of injection to time of evaluation too long/short, evaluator of in duration, etc.)? ☐ Yes ☐ No
(if yes to above, please explain)
If results were positive: Did patient have active TB? ☐ Yes ☐ No
Was patient given prophylactic therapy ☐ Yes ☐ No

MCN:

Drug	Start Date [dd-MMM-yyyy]	Stop Date [dd-MMM-yyyy]

b) Chest X-Ray (CXR) results

Provide CXR results just prior to ustekinumab or any time in past.

Date of CXR: [dd-MMM-yyyy]

Provide CXR results at diagnosis of TB. Date of CXR: [dd-MMM-yyyy]

Provide repeat CXR Results. Date of CXR: [dd-MMM-yyyy]

c. Other laboratory results

Laboratory Test		Test Result	Date: [dd-MMM-yyyy]
AFB Smear	**Sputum**		
	Other (specify)		
	Other (specify		
Culture	**Sputum**		
	Other (specify)		
	Other (specify)		
PCR MTb			
Quantiferon TB Gold			

6. Diagnosis/Treatment

Date of first symptoms of TB: [dd-MMM-yyyy]

Date of diagnosis of TB: [dd-MMM-yyyy]

How much time elapsed from onset of TB symptoms to institution of treatment?

Type of tuberculosis: ☐ Pulmonary ☐ Extrapulmonary: location

☐ Disseminated: location ☐ Multi-drug Resistant TB

MCN:

List treatment regimen below

Medication	Dose/Route of Administration	Start Date /Stop Date [dd-MMM-yyyy]

7. Outcome

What is the patient's current condition?

☐ Patient is alive with no evidence of TB ☐ Patient is alive, but TB is still being treated

☐ Patient died – Date of death: [dd-MMM-yyyy]

Cause of death:

☐ Lost to follow-up

Was **ustekinumab (STELARA®)** re-administered after the event? ☐ Yes ☐ No

If yes, did tuberculosis recur or worsen (list details below)?

ustekinumab (STELARA®) Targeted Follow-up Questionnaire (TFUQ) for Malignancies

Manufacturer Control Number Date of Report [dd-MMM-yyyy]

Person providing this information:			
Name:			
Address:			
City:		State:	ZIP/Postal Code:
Country:		Telephone:	Fax:
Relationship to patient:	☐ Physician	☐ Nurse	☐ Pharmacist
	☐ Other health care professional (please explain)		
	☐ Other (please explain)		
Signature:		Date: [dd-MMM-yyyy]	

Note to LSOs: The following statement may be removed or modified in accordance with local requirements.
For reports originating from the United States: The Health Insurance Portability and Accountability Act (HIPAA) specifically permits covered entities (such as pharmacists, physicians or hospitals) to report adverse events and other information related to the quality, effectiveness and safety of FDA regulated products both to the manufacturers and directly to the FDA.

1. Patient Demographics

Note: If regarding a clinical trial subject, please provide ONLY the demographics under 1a, before completing the rest of the questionnaire.

a. Clinical Trials Only
Patient DOB: [dd-MMM-yyyy] Subject ID Number:
Site ID Number: Protocol Number:

b. Non-Clinical Trials
Patient name:
Patient DOB: [dd-MMM-yyyy] Patient gender: ☐ M ☐ F
Patient's country of origin: Patient height Patient weight lbs kg
Patient's ethnicity: ☐ White ☐ Hispanic ☐ Black ☐ Asian/Pacific Islander
☐ Native American ☐ Unknown

2. ustekinumab (STELARA®) details

Indication for use ☐ Psoriasis ☐ Other (specify)
Dose ☐ 45 mg ☐ 90 mg
Dosing Interval ☐ Every 12 weeks ☐ Other (specify)
Start date [dd-MMM-yyyy] End date [dd-MMM-yyyy]
Approximate total number of injections patient received

MCN:

3. Concomitant medications (attach additional pages as needed)

Medication	Dose/Route of Administration	Start Date / Stop Date [dd-MMM-yyyy]

4. List relevant medical history *(provide prior diagnoses and details for checked items below)*

☐ Previous malignancy ☐ Family history of malignancy
☐ Smoking (specify number of packs years)
☐ History of radiation ☐ History of PUVA (Psoralen + Ultraviolet-A-rays)
☐ Occupational/Exposure ☐ History of excessive alcohol use
☐ Previous administration of immunosuppressive medications (e.g., Methotrexate, cyclosporine, biologics; include drug indication, duration)

5. Diagnosis *(List symptoms and signs, specific diagnosis and how event was diagnosed, include histopathology and staging. Attach relevant report).*

Date of firs symptoms: [dd-MMM-yyyy] Date of diagnosis: [dd-MMM-yyyy]

6. Laboratory and radiology data *(List all relevant laboratory data below, i.e., EBV status. Attach additional pages if needed)*

Laboratory Test	Date [dd-MMM-yyyy]	Results

7. Treatment and response *(List patient treatment regimen and outcome of event below. Include specific treatment, dates of treatment, response to treatment and dates of hospitalization if relevant)*

List patient treatment:

Describe patient outcome (specify cure, partial remission, disease progression, or death):

If no treatment, was there evidence of spontaneous regression:

MCN:

8. Stelara therapy after event

Was **ustekinumab (STELARA®)** discontinued or temporarily interrupted due to the event?
☐ Yes ☐ No
Was **ustekinumab (STELARA®)** re-administered after the event ☐ Yes ☐ No
If yes, did event recur or worsen (list details below)?

9. Comments:

ustekinumab (STELARA®) Targeted Follow-up Questionnaire (TFUQ) for Lymphoma

Manufacturer Control Number: Date of Report [dd-MMM-yyyy]

Person providing this information:			
Name:			
Address:			
City:		State:	ZIP/Postal Code:
Country:		Telephone:	Fax:
Relationship to patient:	☐ Physician	☐ Nurse	☐ Pharmacist
	☐ Other health care professional (please explain)		
	☐ Other (please explain)		
Signature:		Date:	[dd-MMM-yyyy]

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1. Patient Demographics

Note: If regarding a clinical trial subject, please provide ONLY the demographics under 1a, before completing the rest of the questionnaire.

a. Clinical Trials Only
Patient DOB: [dd-MMM-yyyy] Subject ID Number:
Site ID Number: Protocol Number:

b. Non-Clinical Trials
Patient name:
Patient DOB: [dd-MMM-yyyy] Patient gender: ☐ M ☐ F
Patient's country of origin: Patient height Patient weight lbs kg
Patient's ethnicity: ☐ White ☐ Hispanic ☐ Black ☐ Asian/Pacific Islander
☐ Native American ☐ Unknown

2. ustekinumab (Stelara®) Details
Indication for Use (check or circle one): ☐ Plaque Psoriasis ☐ Other, specify
Dose ☐ 45 mg ☐ 90mg Dosing interval ☐ Every 12 weeks ☐ Other (specify)
Start Date: [dd-MMM-yyyy] End date [dd-MMM-yyyy]
Approximate total number of injections patient received:

MCN:

3. **Concomitant medications** *(please attach additional pages if needed)*

Medication	Indication	Dose/route of administration	Start Date/Stop Date [dd-MMM-yyyy]

4. **List relevant medical history** *(provide prior diagnoses and details for items that are checked)*

☐ Family history of malignancy, including malignancy in first degree relatives
☐ History of radiation therapy
☐ History of sun exposure
☐ Occupational/Exposure history
☐ History of PUVA (Psoralen + Ultraviolet-A rays)
☐ Smoking: Current or previous history (*number of pack years*)
☐ History of excessive alcohol use
☐ Any evidence of malignancy prior to starting **ustekinumab** (**STELARA®**) (*specify symptoms and date*)

☐ Previous administration of immunosuppressive medications *(e.g. methotrexate, cyclosporine, biologics: include drug indication, duration)*
☐ Other relevant medical history *(e.g., HIV, RA, SLE, Celiac disease, or inherited immune deficiency disease)*

5. **Lymphoma diagnosis** *(List signs and symptoms and specific histopathologic diagnosis. Please include diagnostic results, including specialty consultations, pathology/histology reports and staging)*

Date of first symptoms: [dd-MMM-yyyy] Date of diagnosis: [dd-MMM-yyyy]

6. **Lymphoma classification** *(List all relevant laboratory data below, e.g., histologic subtype, immunophenotype, cytogenetics. Please attach additional pages if needed)*

7. **Was the lymphoma tissue tested for Epstein-Barr virus (EBV)** *(e.g., by in situ hybridization and/or immunohistologic analysis?)*

☐ No ☐ Yes (please attach report);

If Yes, Test Result: ☐ EBV positive ☐ EBV negative

8. **Treatment** *(List patient treatment regimen below. Include specific treatment, dates of treatment, and dates of hospitalization if relevant.)*

List patient treatment:

If no treatment, was there evidence of spontaneous regression:

9. **ustekinumab (STELARA®) therapy after event**

Was **ustekinumab** (**STELARA®**) discontinued or temporarily interrupted due to the event?
☐ Yes ☐ No

Was **ustekinumab (STELARA®)** re-administered after the event? ☐ Yes ☐ No

MCN:

If yes, did event recur or worsen? *(please list details below)*

10. What is the patient's current condition?

- ☐ The patient is alive with no evidence of lymphoma
- ☐ The patient is alive, but lymphoma is still under treatment
- ☐ The patient has died, date of death [dd-MMM-yyyy]
- ☐ Unknown

11. Comments:

ustekinumab (STELARA®) Targeted Follow-up Questionnaire (TFUQ) for Cardiovascular Events

Manufacturer Control Number Date of Report [dd-MMM-yyyy]

Person providing this information:			
Name:			
Address:			
City:		State:	ZIP/Postal Code:
Country:		Telephone:	Fax:
Relationship to patient:	☐ Physician	☐ Nurse	☐ Pharmacist
	☐ Other health care professional (please explain)		
	☐ Other (please explain)		
Signature:		Date:	[dd-MMM-yyyy]

Note to LSOs: The following statement may be removed or modified in accordance with local requirements.
For reports originating from the United States: The Health Insurance Portability and Accountability Act (HIPAA) specifically permits covered entities (such as pharmacists, physicians or hospitals) to report adverse events and other information related to the quality, effectiveness and safety of FDA regulated products both to the manufacturers and directly to the FDA.

1. **Patient Demographics**

Note: If regarding a clinical trial subject, please provide ONLY the demographics under 1a, before completing the rest of the questionnaire.

a. Clinical Trials Only

Patient DOB: [dd-MMM-yyyy] Subject ID Number:

Site ID Number: Protocol Number:

b. Non-Clinical Trials

Patient name:

Patient DOB: [dd-MMM-yyyy] Patient gender: ☐ M ☐ F

Patient's country of origin: Patient height Patient weight lbs kg

Patient's ethnicity: ☐ White ☐ Hispanic ☐ Black ☐ Asian/Pacific Islander

☐ Native American ☐ Unknown

2. **ustekinumab (STELARA®) details**

Indication for use ☐ Psoriasis ☐ Other (specify)

Dose ☐ 45 mg ☐ 90 mg

Dosing Interval ☐ Every 12 weeks ☐ Other (specify)

Start date [dd-MMM-yyyy] End date [dd-MMM-yyyy]

Approximate total numbers of injections patient received

3. **Concomitant medications** *(attach additional pages as needed)*

Medication	**Dose/Route of Administration**	**Start Date / Stop Date** [dd-MMM-yyyy]

MCN:

4. **List relevant medical history** *(provide prior diagnoses relevant laboratory data [including echo and ischemic evaluation], dates, etc. below)*

☐ Coronary artery disease/Prior MI ☐ Hypertension
☐ Hyperlipidemia/Hypercholesterolemia ☐ Diabetes mellitus ☐ Obesity
☐ Peripheral artery disease ☐ Prior stroke or transient ischemic attack
☐ Congestive heart failure ☐ Prior coronary revascularization / Angioplasty
☐ Family history of early coronary disease/Stroke
☐ Smoking (specify number of pack years
☐ Other cardiac disease (specify)

5. **Diagnosis** *(List symptoms and signs, specify diagnosis and how event was diagnosed)*

Date of first symptoms [dd-MMM-yyyy]
Date of diagnosis [dd-MMM-yyyy]

6. **Laboratory and radiology data** *(List all relevant laboratory data below, including fast lipids and glucose, hemoglobin A1C, cardiac enzymes, as appropriate. Attach additional pages if needed)*

Laboratory Test	**Date** [dd-MMM-yyyy]	**Results**

7. **Treatment and response** *(List any treatments regiment and outcome of event below. Include dates of treatment, response to treatment, and hospitalization dates if relevant)*

Did the event resolve? ☐ Yes ☐ No
If yes, list date that event was considered resolved [dd-MMM-yyyy]
Was **ustekinumab (STELARA®)** discontinued or temporarily interrupted due to the event?
☐ Yes ☐ No
Was **ustekinumab (STELARA®)** re-administered after the event?
☐ Yes ☐ No (If yes, did event recur or worsen (list details below)
Was **ustekinumab (STELARA®)** temporarily interrupted due to event? ☐ Yes ☐ No
If yes, length of time therapy was interrupted ☐ days, ☐ weeks ☐ months

8. **Comments**

ustekinumab (STELARA®) Targeted Follow-up Questionnaire (TFUQ) for Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Manufacturer Control Number Date of Report [dd-MMM-yyyy]

Person providing this information:			
Name:			
Address:			
City:	State:	ZIP/Postal Code:	
Country:	Telephone:	Fax:	
Relationship to patient:	☐ Physician	☐ Nurse	☐ Pharmacist
	☐ Other health care professional (please explain)		
	☐ Other (please explain)		
Signature:	Date: [dd-MMM-yyyy]		

Note to LSOs: The following statement may be removed or modified in accordance with local requirements.
For reports originating from the United States: The Health Insurance Portability and Accountability Act (HIPAA) specifically permits covered entities (such as pharmacists, physicians or hospitals) to report adverse events and other information related to the quality, effectiveness and safety of FDA regulated products both to the manufacturers and directly to the FDA.

1. Patient Demographics

Note: If regarding a clinical trial subject, please provide ONLY the demographics under 1a, before completing the rest of the questionnaire.

a. Clinical Trials Only

Patient DOB: [dd-MMM-yyyy] Subject ID Number:
Site ID Number: Protocol Number:

b. Non-Clinical Trials

Patient name:
Patient DOB: [dd-MMM-yyyy] Patient gender: ☐ M ☐ F
Patient's country of origin: Patient height Patient weight lbs kg
Patient's ethnicity: ☐ White ☐ Hispanic ☐ Black ☐ Asian/Pacific Islander
☐ Native American ☐ Unknown

2. ustekinumab (STELARA®) details

Indication for use ☐ Psoriatic Arthritis ☐ Plaque Psoriasis
☐Other, specify

Dose: ☐ 45 mg ☐ 90mg Dosing interval ☐ Every 12 weeks
Other (specify)

Start date [dd-MMM-yyyy] End date [dd-MMM-yyyy]

Approximate total numbers of injections patient received

MCN:

Action taken with **ustekinumab (STELARA®)** following event:

☐ Discontinued
☐ Interrupted
☐ Dose reduced
☐ Dose increased
☐ Dose not changed
☐ Unknown
☐ Not applicable

Did the event/reaction abate if **ustekinumab (STELARA®)** was withdrawn, interrupted, or reduced?

☐ No ☐ Yes ☐N/A

If **ustekinumab (STELARA®)** was reintroduced, did reaction recur?

☐ No ☐ Yes

Causality assessment -- Is the event/reaction related to **ustekinumab (STELARA®)?**

☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely

3. Prior or concurrent immunosuppressant medications and/ or cytotoxic medications, e.g. Cyclosporin A, interferon alfa, Cisplatin, Tacrolimus, etc.

Medication	Indication	Total Daily Dose	Start Date [dd-MMM-yyyy]	Stop Date [dd-MMM-yyyy]

4. Co-suspect medications (Medications other than Ustekinumab that may have also been related to this/ these event(s)) – Attach additional pages as needed.

Medication	Indication	Dose/route of administration	Start Date/Stop Date [dd-MMM-yyyy]	Lot #

5. Other concomitant medications (Other medications, but you feel are not related to this/ these event[s]) – Attach additional pages as needed.

Medication	Indication	Total Daily Dose	Start Date [dd-MMM-yyyy]	Stop Date [dd-MMM-yyyy]

MCN:

6. List relevant medical history

a) Did the patient have a history of pre-existing systemic Hypertension? ☐ Yes ☐ No

b) Did the patient have a history of pre-existing renal disease (eg. renal failure)? ☐ Yes ☐ No

c) Did the patient have a preceding history infection (eg? HIV) and/ or sepsis? ☐ Yes ☐ No

d) Did the patient have a history of pre-existing immune mediated disease (systemic Lupus erythromatosus, Polyarteritis nodosa etc.)? ☐ Yes ☐ No

e) Other relevant medical history *(transplantation, neurological disorders, pre-eclampsia, chemotherapy etc.):*

7. RPLS diagnosis (List symptoms and signs, and how event was diagnosed below. Attach additional pages as needed)

Date of first symptoms: [dd-MMM-yyyy]
Date to diagnosis: [dd-MMM-yyyy]
Signs:
Symptoms:
Diagnosis:

8. Laboratory and radiology data (Attach additional pages if needed)

a) **MRI: Date:** [dd-MMM-yyyy]
Please indicate the imaging impression

b) **Cerebral angiography: Date:** [dd-MMM-yyyy]

c) **Other relevant test results** *(list additional details below and attach report(s) if available)*

9. Treatment and response *(List any treatment provided, course and outcome)*

10. Comments

Ustekinumab (STELARA®) Targeted Follow-Up Questionnaire (TFUQ) for Venous Thromboembolism (VTE)

Manufacturer Control Number: Date of Report: [dd-MMM-yyyy]

Person providing this information:			
Name:			
Address:			
City:		State:	ZIP/Postal Code:
Country:		Telephone:	Fax:
Relationship to patient:	☐ Physician	☐ Nurse	☐ Pharmacist
	☐ Other health care professional (please explain)		
	☐ Other (please explain)		
Signature:		Date:	[dd-MMM-yyyy]

Note to LSOs: The following statement may be removed or modified in accordance with local requirements.
For reports originating from the United States: The Health Insurance Portability and Accountability Act (HIPAA) specifically permits covered entities (such as pharmacists, physicians or hospitals) to report adverse events and other information related to the quality, effectiveness and safety of FDA regulated products both to the manufacturers and directly to the FDA.

1. Patient Demographics

Note: If regarding a clinical trial subject, please provide ONLY the demographics under 1a, before completing the rest of the questionnaire.

a. Clinical Trials Only

Patient DOB: [dd-MMM-yyyy] Subject ID Number:
Site ID Number: Protocol Number:

b. Non-Clinical Trials/ Other reports

Patient name: (unless prohibited by data privacy/local law)
Patient DOB: [dd-MMM-yyyy] Patient gender: ☐ M ☐ F
Patient's country of origin: Patient height: Patient weight: lbs kg
BMI:
Patient's ethnicity: ☐ White ☐ Hispanic ☐ Black ☐ Asian/Pacific Islander
☐ Native American ☐ Unknown

MCN:

2. Ustekinumab (STELARA®) Details

Indication for use:
Dose/unit/frequency at time of event:
Route/formulation:
Start date: [dd-MMM-yyyy], End date: [dd-MMM-yyyy]
Recent dose change? (Elaborate on timing/amount of dose change):
Lot #:

Co-suspect medications – Attach additional pages as needed.

Medication	Indication	Dose/route of administration	Start Date/Stop Date [dd-MMM-yyyy]	Lot #

Concomitant medications – Attach additional pages as needed.

Medication	Indication	Dose/route of administration	Start Date/Stop Date [dd-MMM-yyyy]	Lot #

Relevant medications used in the past – Attach additional pages as needed.

Medication	Indication	Dose/route of administration	Start Date/Stop Date [dd-MMM-yyyy]	Lot #

3. Medical History and Concurrent Conditions

Please provide details:

Is the patient overweight or obese?	☐ No	☐ Yes – details:
Does the patient drink alcohol?	☐ No	☐ Yes – details:
Is there a history of drug abuse?	☐ No	☐ Yes – details:
Is there a history of cancer?	☐ No	☐ Yes – details:
Is there a prior history of DVT/PE/VTE?	☐ No	☐ Yes – details:
Is there a history of blood transfusion?	☐ No	☐ Yes – details:
Does the patient smoke?	☐ No	☐ Yes – details:
Was the patient pregnant at the time of event?	☐ No	☐ Yes – details:

MCN:

Is there a history of cardiovascular disorder? ☐ No ☐ Yes – details:
Is there a history of organ transplantation? ☐ No ☐ Yes – details:

List relevant family history:

Concurrent conditions:
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.)
☐ Dehydration
☐ Recent surgery
☐ Concomitant oral contraceptive use
☐ Phlebitis
☐ Inflammatory bowel disease
☐ Diabetes mellitus
☐ Hypertension
☐ Other significant medical co-morbidities
☐ Recent trauma
☐ Recent discontinuation of warfarin
☐ Hormone replacement therapy
☐ Indwelling central venous catheters
☐ Lupus
☐ Myeloproliferative disorders
☐ Hyperlipidemia

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

4. Adverse Event Description

Details and course of the adverse event:
Start date of the event: [dd-MMM-yyyy]
Patient's signs and symptoms

☐ Leg/Calf Oedema ☐ Pain in Leg/Calf ☐ Haemoptysis
☐ Dyspnoea ☐ Chest Pain/Discomfort ☐ Syncope
☐ Tachypnoea ☐ Tachycardia ☐ Cough
☐ Other symptoms:

Was patient on VTE prophylaxis? ☐ No ☐ Yes, details:
Is the event serious?
If yes, please clarify the seriousness criteria:
Caused hospitalization?
Was medically significant?
Was life-threatening?
Was fatal?
Caused disability?
Due to congenital anomaly?

MCN:

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

Diagnostic Test	Results at baseline or prior to use of Stelara® (Include date and value/details)	Test results after use of Stelara® (Include date and value/details)
Clotting Profile		
D-Dimer Levels		
Troponins		
Brain Natriuretic Peptide		
Arterial Blood Gas		
Chest X-Ray		
Electrocardiography		
Echocardiography		
Duplex Ultrasonography		
Contrast Venography		
Pulmonary Angiography		
Ventilation-Perfusion Scanning		

Please provide details of any additional diagnostic results:

6. **Treatment and Outcome**

Patient was treated after the event? ☐ No ☐ Yes (Details of treatment:)

Outcome:

☐ Recovered ☐ Recovering ☐ Not recovered ☐ Fatal ☐ Unknown

Please provide details (including any applicable dates): (dd/MMM/yyyy)

Action taken with ustekinumab (STELARA®) following event:

☐ Discontinued ☐ Interrupted ☐ Dose reduced ☐ Dose increased

☐ Dose not changed ☐ Unknown ☐ Not applicable

Did the event/reaction abate after ustekinumab (STELARA®) was withdrawn, interrupted, or reduced?

☐ No ☐ Yes

If ustekinumab (STELARA®) was reintroduced, did reaction recur?

☐ No ☐ Yes

MCN:

Causality assessment – Is the event/reaction related to ustekinumab (STELARA®)?

☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely

Causality assessment – Is the event/reaction related to any other condition or medications?

☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely

Details:

7. Comments/Any other details

Annex 5: Protocols for Proposed and Ongoing Studies in RMP Part IV

Not applicable.

Annex 6: Details of Proposed Additional Risk Minimization Activities

Not applicable.

Annex 7: Other Supporting Data (Including Referenced Material)

Annex 7.1 References

Annex 7.1.1 Key References

Airoldi I, Di Carlo E, Cocco C, et al. Lack of Il12rb2 signaling predisposes to spontaneous autoimmunity and malignancy. Blood. 2005;106:3846-3853.

Bowman EP, Chackerian AA, Cua DJ. Rationale and safety of anti-interleukin-23 and anti-interleukin-17A therapy. Curr Opin Infect Dis. 2006;19(3):245-252.

Brunda MJ, Luistro L, Warrier RR, et al. Antitumor and Antimetastatic Activity of Interleukin 12 against Murine Tumors. J Exp Med. 1993;178:1223-1230.

Kappelman MD, Horvath-Puho E, Sandler RS, et al. Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study. Gut. 2011;60(7):937-943.

Torti DC, Feldman SR. Interleukin-12, interleukin-23, and psoriasis: Current prospects. J Am Acad Dermatol. 2007;57(6):1059-1068.

Vegh Z, Golovics PA, Lovasz BD, et al. Low incidence of venous thromboembolism in inflammatory bowel diseases: prevalence and predictors from a population-based inception cohort. Scand J Gastroenterol. 2015;50(3):306-311.

Annex 7.1.2 Other References

Abuabara K, Azfar RS, Shin DB et al. Cause-specific mortality in patients with severe psoriasis: a population-based cohort study in the U.K. Br J Dermatol. 2010;163(3):586-92.

Acosta-Rodriguez EV, Rivino L, Geginat J, et al. Surface phenotype and antigenic specificity of human interleukin 17-producing T helper memory cells. Nat Immunol. 2007;8(6):639-646.

Allen JA, Adlakha A, Bergethon PR. Reversible posterior leukoencephalopathy syndrome after bebacizumab/FOLFIRI regimen for metastatic colon cancer. Arch Neurol. 2006;63:1475-1478.

Alkim H, Koksal AR, Boga S, Sen I, Alkim C. Etiopathogenesis, Prevention, and Treatment of Thromboembolism in Inflammatory Bowel Disease. Clin Appl Thromb Hemost. 2017;23(6):501-510.

Andrejak C, Andréjak C, Nielsen R, et al. Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. Thorax. 2013;68(3):256-262.

Aniwan S, Park SH, Loftus EV Jr. Epidemiology, Natural History, and Risk Stratification of Crohn's Disease. Gastroenterol Clin North Am. 2017;46(3):463-480.

Augustin M, Glaeske G, Radtke MA, Christophers E, Reich K, Schafer I. Epidemiology and comorbidity of psoriasis in children. Br J Dermatol. 2010;162(3):633-636.

Avastin® [Prescribing Information]. South San Francisco, CA: Genentech, Inc;2009.

Bartynski WS. Posterior reversible encephalopathy syndrome, Part 1: fundamental imaging and clinical features. AJNR Am J Neuroradiol. 2008;29:1036-1042.

Bernstein CN, Hitchon CA, Walld R, et al. Increased Burden of Psychiatric Disorders in Inflammatory Bowel Disease. Inflamm Bowel Dis. 2019;25(2):360-368.

Bostoen J, Van Praet L, Brochez L, et al. A cross-sectional study on the prevalence of metabolic syndrome in psoriasis compared to psoriatic arthritis. J Eur Acad Dermatol Venereol. 2014;28(4):507-511.

Bronckers IMGJ, Paller AS, van Geel MJ, et al. Psoriasis in Children and Adolescents: Diagnosis, Management and Comorbidities. Paediatric Drugs. 2015;17:373-384.

Brunet E, Roig-Ramos C, Vela E, et al. Prevalence, incidence and mortality of inflammatory bowel disease in Catalonia. A population-based analysis. Ann Med. 2018;50(7): 613-619.

Buckley C, Cavill C, Taylor G, et al. Mortality in psoriatic arthritis: a single-center study from the UK. J Rheumatol. 2010;37:2141-2144.

Burden-Teh E, Thomas KS, Ratib S, et al. The epidemiology of childhood psoriasis: a scoping review. British Journal of Dermatology. 2016;174(6):1242-1257.

Burisch J, Jess T, Martinato M, et al. The burden of inflammatory bowel disease in Europe. J Crohns Colitis. 2013;7(4):322-337.

Burisch J, Munkholm P. The epidemiology of inflammatory bowel disease. Scand J Gastroenterol. 2015;50(8):942-951.

Cárdenes M, Angel-Moreno A, Fieschi C, et al. Oesophageal squamous cell carcinoma in a young adult with IL-12R beta 1 deficiency. J Med Genet. 2010;47(9):635-637.

Cassidy PM, Hedberg K, Saulson A, et al. Nontuberculous mycobacterial disease prevalence and risk factors: a changing epidemiology. Clin Infect Dis, 2009;49(12): e124-129.

Cosnes J, Gower-Rousseau C, Seksik P, et al. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology. 2011;140(6):1785-1794.

Cueto Torreblanca IR, Camargo Camero R, Andrade Bellido E, et al. Epidemiology of inflammatory bowel disease in Malaga: incidence rate and follow-up of a cohort diagnosed between 2007-2008. Rev Esp Enferm Dig 2017;109(8):572-577.

Christophers E, Barker JN, Griffiths CE, et al. The risk of arthritis remains constant following initial diagnosis of psoriasis among patients seen in European dermatology clinics. J Eur Acad Dermatol Venereol. 2010;24(5):548-554.

Chouraki V, Savoye G, Dauchet L, et al. The changing pattern of Crohn's disease incidence in northern France: a continuing increase in the 10- to 19-year old age bracket (1988-2007). Aliment Pharmacol Ther. 2011;33(10):1133-1142.

Colombo MP, Trinchieri G. Interleukin-12 in anti-tumor immunity and immunotherapy. Cytokine Growth Factor Rev. 2002;13:155-168.

Cury DB, Moss AC, Schor N. Nephrolithiasis in patients with inflammatory bowel disease in the community. Int J Nephrol Renovasc Dis. 2013;6:139-142.

Damas OM, Deshpande AR, Avalos DJ, et al. Treating Inflammatory Bowel Disease in Pregnancy: The Issues We Face Today. J Crohns Colitis. 2015;9(10):928-936.

Danese S, Papa A, Saibeni S, Repici A, Malesci A, Vecchi M. Inflammation and coagulation in inflammatory bowel disease: The clot thickens. Am J Gastroenterol. 2007;102(1):174-186.

Day M, Nam D, Goodman S, et al. Psoriatic arthritis. J Am Acad Orthop Surg. 2012;20:28-37.

de Groof EJ, Rossen NG, van Rhijn BD, et al. Burden of disease and increasing prevalence of inflammatory bowel disease in a population-based cohort in the Netherlands. Eur J Gastroenterol Hepatol. 2016;28(9):1065-1072.

Dika E, Bardazzi F, Balestri R, et al. Environmental factors and psoriasis. Curr Probl Dermatol. 2007;35:118-135.

Dregan A, Charlton J, Chowienczyk P, et al. Chronic inflammatory disorders and risk of type 2 diabetes mellitus, coronary heart disease, and stroke: a population-based cohort study. Circulation. 2014;130(10):837-844.

Eder L, Chandran V, and Gladman DD. What have we learned about genetic susceptibility in psoriasis and psoriatic arthritis? Curr Opin Rheumatol. 2015;27(1):91-98.

Egeberg AL, Skov GH, Gislason JP, et al. Incidence and Prevalence of Psoriasis in Denmark. Acta Derm Venereol. 2017a;97(7):808-812.

Egeberg AL, Kristensen JP, Thyssen GH, et al. Incidence and prevalence of psoriatic arthritis in Denmark: a nationwide register linkage study. Ann Rheum Dis. 2017b;76(9):1591-1597.

Eichenfield LF, Paller AS, Tom WL, et al. Pediatric psoriasis: Evolving perspectives. Pediatr Dermatol. 2018;35(2):170-181.

Eriksson CY, Cao S, Rundquist Y, et al. Changes in medical management and colectomy rates: a population-based cohort study on the epidemiology and natural history of ulcerative colitis in Orebro, Sweden, 1963-2010. Aliment Pharmacol Ther. 2017;46(8):748-757.

Fancher T, Kravitz R. In the clinic. Depression. Ann Intern Med. 2007;ITC5-1-ITC5-16.

FDA Guidance for Industry: Pharmacokinetics in patients with impaired hepatic function: study design, data analysis, and impact on dosing and labeling. Rockville, MD:US Dept of Health and Human Services, Food and Drug Administration;May 2003.

FDA Guidance for Industry: Pharmacokinetics in patients with impaired renal function - study design, data analysis, and impact on dosing and labeling. Rockville, MD:US Dept of Health and Human Services, Food and Drug Administration;May 1998.

FDA Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials;September 2005.

Feuerstein JD, Cheifetz AS. Crohn Disease: Epidemiology, Diagnosis, and Management. Mayo Clin Proc. 2017;92(7):1088-1103.

Fieschi C, Casanova JL. The role of interleukin-12 in human infectious diseases: only a faint signature. Eur J Immunol. 2003;33(6):1461-1464.

Filipe-Santos O, Bustamante J, Chapgier A, et al. Inborn errors of IL-12/23- and IFN-γ-mediated immunity: molecular, cellular, and clinical features. Semin Immunol. 2006;18:347-361.

Finsterer J. Management of peripheral facial nerve palsy. Eur Arch Otorhinolaryngol. 2008;265:743-752.

Fry L, Baker BS. Triggering psoriasis: the role of infections and medications. Clin Dermatol. 2007;25(6):606-615.

Fumery M, Singh S, Dulai PS, et al. Natural History of Adult Ulcerative Colitis in Population-based Cohorts: A Systematic Review. Clin Gastroenterol Hepatol. 2018;16(3):343-356.

Gajendran M, Loganathan P, Jimenez G, et al. A comprehensive review and update on ulcerative colitis. Dis Mon. 2019;65(12):100851.

Gelfand JM, Gladman DD, Mease PJ, et al. Epidemiology of psoriatic arthritis in the population of the US. J Am Acad Dermatol. 2005;53(4):573.

Gelfand JM, Neimann AL, Shin DB et al. Risk of myocardial infarction in patients with psoriasis. JAMA. 2006;296(14):1735-1741.

Gladman DD, Antoni C, Mease P, et al. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005;64(Suppl 2): ii14-ii17.

Gladman DD, Ang M, Su L, Tom BD, et al. Cardiovascular morbidity in psoriatic arthritis. Ann Rheum Dis. 2009 Jul;68(7):1131-5.

Gladman DD. Psoriatic arthritis. Dermatol Ther. 2009. 22(1):40-55.

Gladman DD. Recent advances in understanding and managing psoriatic arthritis. F1000Research 5:2016;2670.

Global Burden of Disease Study. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet. 2017;390(10100):1211-1259.

Haddad, A, Zisman D. Comorbidities in Patients with Psoriatic Arthritis. Rambam Maimonides Medical Journal 2017;8(1):e0004.

Happel KI, Dubin PJ, Zheng M, et al. Divergent roles of IL-23 and IL-12 in host defense against Klebsiella pneumoniae. J Exp Med. 2005;202(6):761-769.

Helmick CG, Lee-Han H, Hirsch SC, et al. Prevalence of psoriasis among adults in the US: 2003-2006 and 2009-2010 National Health and Nutrition Examination Surveys. Am J Prev Med. 2014;47(1):37-45.

Hilsinger RL Jr, Adour KK, Doty HE. Idiopathic facial paralysis, pregnancy, and the menstrual cycle. Ann Otol Rhinol Laryngol. 1975;84(4 Pt 1):433-442.

Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. N Engl J Med. 1996;334:494-500.

Holland NJ, Weiner GM. Recent developments in Bell's palsy. BMJ. 2004;329:553–557.

Hovde O, Kempski-Monstad I, Samstuen MC et al. Mortality and causes of death in Crohn's disease: results from 20 years of follow-up in the IBSEN study. Gut. 2013:1-5.

Hovde O, Moum BA. Epidemiology and clinical course of Crohn's disease: Results from observational studies. World J Gastroenterol. 2012;18(15):1723-1731.

Husted JA, Thavaneswaran A, Chandran V, et al. Cardiovascular and other comorbidities in patients with psoriatic arthritis: a comparison with patients with psoriasis. Arthritis Care Res (Hoboken). 2011;63(12):1729-1735.

Icen M, Crowson CS, McEvoy MT, et al. Trends in incidence of adult-onset psoriasis over three decades: a population-based study. J Am Acad Dermatol 2009;60:394-401.

Jussila A, Virta LJ, Pukkala E, et al. Mortality and causes of death in patients with inflammatory bowel disease: a nationwide register study in Finland. J Crohns Colitis. 2014;8(9):1088-1096.

Jussila A, Virta LJ, Kautiainen H, Rekiaro M, Nieminen U, Färkkilä MA. Increasing incidence of inflammatory bowel diseases between 2000 and 2007: A nationwide register study in Finland. Inflamm Bowel Dis. 2012;18(3):555-561.

Kanerva M, Nissinen J, Moilanen K, et al. Microbiologic findings in acute facial palsy in children. Otol Neurotol. 2013;34(7):e82-87.

Kastrup O, Diener HC. TNF-antagonist etanercept induced reversible posterior leukoencephalopathy syndrome. J Neurol. 2008;255:452-453.

Khader SA, Pearl JE, Sakamoto K, et al. IL-23 compensates for the absence of IL-12p70 and is essential for the IL-17 response during tuberculosis but is dispensable for protection and antigen-specific IFN-gamma responses if IL-12p70 is available. J Immunol. 2005;175(2):788-795.

Kleinschek MA, Muller U, Brodie SJ, et al. IL-23 Enhances the inflammatory cell response in cryptococcus neoformans infection and induces a cytokine pattern distinct from IL-12. J Immunol. 2006;176(2):1098-1106.

Kristensen SL, Ahlehoff O, Lindhardsen J, et al. Disease activity in inflammatory bowel disease is associated with increased risk of myocardial infarction, stroke and cardiovascular death--a Danish nationwide cohort study. PLoS One. 2013;8(2):e56944.

Landau JL, Moody MN, Kazakevich N, et al. Psoriasis and the pregnant woman: what are the key considerations? Skin Therapy Lett. 2011;16(9):1-3.

Lashner B. Crohn's Disease. Cleveland Clinic. http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/gastroenterology/crohns-disease/. Published Jan 2013. Accessed Sept. 18, 2017.

Lawley LP, McCall CO, Lawley TJ. Chapter 52. Eczema, Psoriasis, Cutaneous Infections, Acne, and Other Skin Disorders. In: Fauci AS, Kasper DL, Jameson JL, Longo DL, Hauser SL, eds. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw-Hill; 2012. Accessed 01 October 2012.

Lebwohl M. Psoriasis. The Lancet. 2003;361(9364):1197-1204.

Lebwohl MG, Bachelez H, Barker J, et al. Patient perspectives in the management of psoriasis: results from the population-based multinational assessment of psoriasis and psoriatic arthritis survey. J Am Acad Dermatol. 2014;70(5): 871-81.e1-30.

Lee VH, Wijdicks EFM, Manno EM, et al. Clinical spectrum of reversible posterior leukoencephalopathy syndrome. Arch Neurol. 2008;65(2):205-210.

Li W-Q, Han J-L, Manson JE, et al. Psoriasis and risk of nonfatal cardiovascular disease in U.S. women: a cohort study. Br J Dermatol. 2012;166:811-818.

Loftus EV. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology. 2004;126(6):1504–1517.

Lophaven SN, Lynge E, Burisch J. The incidence of inflammatory bowel disease in Denmark 1980-2013: a nationwide cohort study. Aliment Pharmacol Ther. 2017;45(7):961-972.

Lovasz BD, Lakatos L, Horvath A, et al. Evolution of disease phenotype in adult and pediatric onset Crohn's disease in a population-based cohort. World J Gastroenterol. 2013;19(14):2217-2226.

Manninen P, Karvonen AL, Huhtala H, et al. Mortality in ulcerative colitis and Crohn's disease. A population-based study in Finland. J Crohns Colitis. 2012;6(5):524-528.

Matusiewicz D, Koerber A, Schadendorf D, et al. Childhood psoriasis – an analysis of German health insurance data. Pediatr Dermatol. 2014;31(1):8-13.

Mayo Clinic 2018. Crohn's Disease. Retrieved 9 April 2018, from https://www.mayoclinic.org/diseases-conditions/crohns-disease/diagnosis-treatment/drc-20353309.

Mayo Clinic, 2011. Crohn's Disease: Risk Factors. Available: http://www.mayoclinic.com/health/crohns-disease/DS00104/DSECTION=risk-factors. Accessed 1 July 2013.

Mayo Clinic 2011. Crohn's disease: Treatments and drugs, Available: http://www.mayoclinic.com/health/crohns-disease/DS00104/DSECTION=treatments-and-drugs. Accessed 1 July 2013.

Mayo Clinic 2018. Psoriasis. Retrieved 9 April 2018. Available: https://www.mayoclinic.org/diseases-conditions/psoriasis/symptoms-causes/syc-20355840.

Mayo Clinic. Psoriasis: risk factors. Available at http://www.mayoclinic.org/diseases-conditions/psoriasis/basics/risk-factors/con-20030838. Accessed June 18, 2014.

Mayo Clinic 2014. Salmonella infections: risk factors. Available at: http://www.mayoclinic.org/diseases-conditions/salmonella/basics/risk-factors/con-20029017. Accessed June 30, 2014.

Mayo Clinic 2018. Ulcerative colitis: Risk Factors. Available at: http://www.mayoclinic.com/health/ulcerative-colitis/DS00598/DSECTION=risk-factors. Accessed 9 April 2018.

Mayo Clinic 2018. Ulcerative colitis. Available at: https://www.mayoclinic.org/diseases-conditions/ulcerative-colitis/symptoms-causes/syc-20353326. Accessed 9 April 2018.

Mayo Clinic 2018. Ulcerative colitis: Diagnosis and Treatment. Available at: https://www.mayoclinic.org/diseases-conditions/ulcerative-colitis/diagnosis-treatment/drc-20353331. Accessed 9 April 2018.

Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142(1):46-54.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMSb). Diseases. (March 2017). Psoriasis. Retrieved Aug. 17, 2017, from https://www.niams.nih.gov/Health_Info/Psoriasis/default.asp.

National Institute of Diabetes and Digestive & Kidney Disease (NIDDK). (2017). Crohn's Disease. Retrieved Aug. 16, 2017, from https://www.niddk.nih.gov/health-information/digestive-diseases/crohns-disease.

National Psoriasis Foundation, 2014. Pustular Psoriasis. Available at https://www.psoriasis.org/about-psoriasis/types/pustular. Accessed on June 30, 2014.

Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol. 2006;55(5):829-835.

Ng, SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2018;390(10114):2769-2778.

Nguyen GC, Bernstein CN, Bitton A, et al. Consensus Statements on the Risk, Prevention, and Treatment of Venous Thromboembolism in Inflammatory Bowel Disease: Canadian Association of Gastroenterology. Gastroenterology. 2014;146(3):835-848.e6.

Novelli F, Casanova JL. The role of IL-12, IL-23 and IFN-gamma in immunity to viruses. Cytokine Growth Factor Rev. 2004;15(5):367-377.

O'Brien DP, Currie BJ, Krause VL. Nontuberculous mycobacterial disease in Northern Australia: A case series and review of the literature. Clin Infect Dis. 2000;31(4):958-967.

Ogdie A, et al. Prevalence and treatment patterns of psoriatic arthritis in the UK. Rheumatology (Oxford). 2013;52(3): 568-575.

Ogdie A, Haynes K, Troxel AB, et al. Risk of mortality in patients with psoriatic arthritis, rheumatoid arthritis and psoriasis: a longitudinal cohort study. Ann Rheum Dis. 2014;73(1):149-153.

Ogdie AS, Maliha D, Shin T, et al. Cause-specific mortality in patients with psoriatic arthritis and rheumatoid arthritis. Rheumatology (Oxford). 2017;56(6):907-911.

O'Toole A, Walsh P, Keegan D, et al. Mortality in inflammatory bowel disease patients under 65 years of age. Scand J Gastroenterol. 2014;49(7):814-819.

Ozden MG, Tekin NS, Gürer MA, et al. Environmental risk factors in pediatric psoriasis: a multicenter case-control study. Pediatr Dermatol, 2011;28(3): 306-312.

Paller AS, Singh R, Cloutier M, et al. Prevalence of Psoriasis in Children and Adolescents in the United States: A Claims-Based Analysis. J Drugs Dermatol. 2018;17(2):187-194.

Papa A, Gerardi V, Marzo M, et al. Venous thromboembolism in patients with inflammatory bowel disease: Focus on prevention and treatment. World J Gastroenterol. 2014;20(12):3173-3179.

Paolino E, Granieri E, Tola MR, et al. Predisposing factors in Bell's palsy: a case-control study. J Neurol. 1985;232:363–365.

Parisi R, Symmons DP, Griffiths CE, et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2013;133(2): 377-85.

Pecket P, Schattner A. Concurrent Bell's palsy and diabetes mellitus: a diabetic mononeuropathy? J Neurol Neurosurg Psychiatry. 1982;45:652-655.

Peitersen E. Bell's palsy: the spontaneous course of 2,500 peripheral facial nerve palsies of different etiologies. Acta Otolaryngol Suppl. 2002;549:4-30.

Piovani D, Danese S, Peyrin-Biroulet L, et al. Environmental Risk Factors for Inflammatory Bowel Diseases: An Umbrella Review of Meta-analyses. Gastroenterology. 2019;157(3):647-659.

Pouplard C, Brenaut E, Horreau C, et al. Risk of cancer in psoriasis: a systematic review and meta-analysis of epidemiological studies. J Eur Acad Dermatol Venereol. 2013;Suppl 3:36-46.

Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. J Am Acad Dermatol. 2014;70(3):512-516.

Rajasekhar A, George TJ Jr. Gemcitabine-induced reversible posterior leukoencephalopathy syndrome: a case report and review of the literature. Oncologist. 2007;12:1332-1335.

Rao KL, Varalakshmi C, Ali AM, et al. Administration of anti-IL-12 antibody in vivo inhibits rejection of a rat histiocytoma and suppresses cytokine response in a tumor-bearing host. Immunology. 1997;92(3):381-387.

Reed C, von Reyn CF, Chamblee S, et al. Environmental risk factors for infection with Mycobacterium avium complex. Am J Epidemiol. 2006;164(1):32-40.

Román ALS, Muñoz F. Comorbidity in inflammatory bowel disease. World Journal of Gastroenterology: WJG. 2011;17(22):2723-2733.

Salahadeen E, Torp-Pedersen C, Gislason G, et al. Nationwide population-based study of cause-specific death rates in patients with psoriasis. J Eur Acad Dermatol Venereol. 2015 May;29(5):1002-1005.

Scotti L, Franchi M, Marchesoni A, et al. Prevalence and incidence of psoriatic arthritis: A systematic review and meta-analysis. Semin Arthritis Rheum. 2018;epub ahead of print.

Setty A, Choi HK. Psoriatic arthritis epidemiology. Curr Rheumatol Rep. 2007;9:449-454.

Shah SC, Khalili H, Gower-Rousseau C, et al. Sex-Based Differences in Incidence of Inflammatory Bowel Diseases-Pooled Analysis of Population-Based Studies From Western Countries. Gastroenterology. 2018;155(4):1079-1089.

Sjöberg D, Holmstrom T, Larsson M, et al. Incidence and natural history of ulcerative colitis in the Uppsala Region of Sweden 2005-2009- results from the IBD cohort of the Uppsala Region (ICURE). J Crohns Colitis. 2013;7(9):e351-e357.

Sonnenberg A. Age distribution of IBD hospitalization. Inflamm Bowel Dis. 2010;16(3):452-457.

Springate DA, Parisi R, Kontopantelis E, et al. Incidence, prevalence and mortality of patients with psoriasis: a U.K. population-based cohort study. Br J Dermatol. 2017;176(3):650-658.

Steinwurz F, Denadai R, Saad-Hossne R, et al. Infliximab-induced psoriasis during therapy for Crohn's disease. J Crohns Colitis. 2012;6(5):610-616.

Tobin AM, Veale DJ, Fitzgerald O, et al. Cardiovascular Disease and Risk Factors in Patients with Psoriasis and Psoriatic Arthritis. J of Rheumatol. 2010;37:1386-1394.

Tollefson MM, Crowson CS, McEvoy MT, et al. Incidence of psoriasis in children: a population-based study. J Am Acad Dermatol. 2010;62(6): 979-87.

Tollefson MM. Diagnosis and management of psoriasis in children. Pediatr Clin North Am. 2014;61(2): 261-277.

Trinchieri G. Interleukin-12 and the regulation of innate resistance and adaptive immunity. Nat Rev Immunol. 2003;3(2):133-146.

Velcade® [Prescribing Information]. Cambridge, MA: Millennium Pharmaceuticals, Inc.;2008.

Vena GA, Altomare G, Ayala F, et al. Incidence of psoriasis and association with comorbidities in Italy: a 5-year observational study from a national primary care database. Eur J Dermatol. 2010;20(5):593-598.

Wilson FC, Icen M, Crowson CS, et al. Time trends in epidemiology and characteristics of psoriatic arthritis over 3 decades: a population-based study. J Rheumatol. 2009;36:361-367.

World Health Organization (2016). Global Report on Psoriasis. Geneva Switzerland.

Ye Y, Pang Z, Chen W, Ju S, Zhou C. The epidemiology and risk factors of inflammatory bowel disease. Int J Clin Exp Med. 2015;8(12):22529-22542.

Yeung H, Takeshita J, Mehta NN, et al. Psoriasis severity and the prevalence of major medical co-morbidities: a population-based study. JAMA Dermatol. 2013;149(10):1173-1179.

Zamvar V, Sugarman ID, Tawfik RF, et al. Posterior reversible encephalopathy syndrome following infliximab infusion. J Pediatr Gastroenterol Nutr. 2009;48:102-105.

Zezos P, Kouklakis G, Saibil F. Inflammatory bowel disease and thromboembolism. World J Gastroenterol. 2014;20(38):13863-13878.

Annex 7.2 Abbreviations

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADR	adverse drug reaction
AE	adverse event
AZA	azathioprine
BCG	Bacillus-Calmette-Guérin
BMI	body mass index
BSA	body surface area
CD	Crohn's disease
CI	confidence interval
CPRD	Clinical Practice Research Datalink
CV	cardiovascular
DMARD	disease-modifying anti-rheumatic drug
DNA	deoxyribonucleic acid
EMA	European Medicines Agency
EU	European Union
HCP	healthcare professional
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLT	high level term
HR	hazard ratio
IBD	inflammatory bowel disease
ICD	International Classification of Diseases and Related Health Problems
ICH	International Council for Harmonisation
IL	interleukin
IV	intravenous
LMP	last menstrual period
LTE	long-term extension
mAb	monoclonal antibody
MAC	*Mycobacterium avium/Mycobacterium intracellulare* complex
MACE	major adverse cardiovascular event
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MTX	methotrexate
NMSC	non-melanoma skin cancer
NOAEL	no-observed-adverse-effect level
NSAID	non-steroidal anti-inflammatory drug
NTM	non-TB mycobacterial
OR	odds ratio
PASS	postauthorization safety study
PBRER	Periodic Benefit Risk Evaluation Report
PIP	Pediatric Investigational Plan
PK	pharmacokinetic
PRAC	Pharmacovigilance Risk Assessment Committee
PsA	psoriatic arthritis
PSOLAR	PSOriasis Longitudinal Assessment and Registry
PSUR	Periodic Safety Update Report
PT	preferred term
PUVA	psoralen and ultraviolet A
PY	person-year(s)

RMP	Risk Management Plan
RPLS	reversible posterior leukoencephalopathy syndrome
SC	subcutaneous
SLE	systemic lupus erythematosus
SmPC	Summary of Product Characteristics (EU)
SMQ	Standardized MedDRA Query
SMR	standardized mortality ratio
SNDS	French National Health Data System
SOC	system organ class
SWIBREG	Swedish National Quality Register for Inflammatory Bowel Disease
TB	tuberculosis
TFUQ	targeted follow-up questionnaire
THIN	The Health Information Network
TNF	tumor necrosis factor
UC	ulcerative colitis
UK	United Kingdom
US	United States
UV	ultraviolet
VTE	venous thromboembolism

Annex 7.3 MedDRA Search Strategy

The following are the MedDRA search terms used in the database search for each important identified risk and important potential risk, which are presented in the tables in Section SVII.3 and include data from the Phase 1, 2 and 3 clinical trials.

Serious systemic hypersensitivity reactions

- Anaphylactic PTs: Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock, and Type I hypersensitivity
- Serum sickness PTs: Serum sickness and Serum sickness-like reaction.

Facial palsy

- Facial paralysis

Pustular psoriasis

- Pustular psoriasis and Palmoplantar pustulosis

Erythrodermic psoriasis

- Erythrodermic psoriasis

Serious infections (including mycobacterial and salmonella infections)

- Serious infections included all SAEs judged to be an infection by the investigator regardless of the system organ class (SOC) to which the SAE was coded. Events of atypical salmonella and atypical mycobacterial infection were identified based on all PTs included in the HLTs of Salmonella infections and Atypical mycobacterial infections.

Malignancy

- Events of malignancy (both NMSC and other malignancies) were identified by medical review by MAH physicians through a subject-level review of all events reported in the SOC of Neoplasms benign, malignant and unspecified.

Cardiovascular events

- Cardiovascular events were defined as serious MACEs (cardiovascular death, non-fatal MI, or non-fatal stroke) and were either independently adjudicated or were identified by internal clinical review by MAH physicians. The clinical review includes clinical trial SAEs occurring in the SOCs of Cardiac disorders, Nervous system disorders, Investigations, Vascular disorders, and all cardiovascular deaths and deaths of unknown cause.

Serious depression including suicidality

- Events of serious depression and suicidality were identified by medical review by sponsor physicians of all deaths and SAEs occurring in the SOCs of Injury, poisoning and procedural complications; General disorders and administration site conditions; Psychiatric disorders; and Social circumstances

Reversible posterior leukoencephalopathy syndrome

- Posterior reversible encephalopathy syndrome

Venous thromboembolism

- SMQ (Embolic and thrombotic events, venous)

Exposure During Pregnancy

- The global safety database was searched for medically confirmed and medically unconfirmed cases received that may have involved exposure during pregnancy or lactation. The following search criteria were used:
  - Cases with a classification of pregnancy exposure/pregnancy
  - Cases with a classification of parent/child
  - Cases in which the patient age group is “neonate” or “infant”
  - Cases in which the patient is a child aged ≤2 years
  - Cases coding to either of the follows SOCs: Congenital, Familial and Genetic Disorders and Pregnancy, Puerperium and Perinatal Conditions
  - Cases coding to any of the PTs associated with pregnancy or lactation identified following review of summary tabulations.

Annex 7.4 PTs from Risks

The following are the PTs reported in the clinical trials noted in Section SVII.3.1 for each important identified risk and important potential risk.

Serious systemic hypersensitivity reactions

Anaphylactic reaction, Anaphylactoid reaction, Serum sickness-like reaction.

Facial palsy

Facial paralysis.

Pustular psoriasis

Palmoplantar pustulosis, Pustular psoriasis.

Erythrodermic psoriasis

Erythrodermic psoriasis.

Serious infections (including mycobacterial and salmonella infections)

Abdominal abscess, Abdominal infection, Abdominal pain, Abdominal pain lower, Abscess intestinal, Acarodermatitis, Acute respiratory failure, Acute sinusitis, Anal abscess, Anal fistula infection, Appendicitis, Appendicitis perforated, Arthritis, Arthritis bacterial, Asymptomatic HIV infection, Bacteraemia, Beta haemolytic streptococcal infection, Bronchitis, Bronchitis chronic, Campylobacter gastroenteritis, Campylobacter infection, Cellulitis, Cholangitis, Cholecystitis, Cholecystitis acute, Clostridium difficile colitis, Clostridium difficile infection, Colitis, Complicated appendicitis, Crohn's disease, Cytomegalovirus colitis, Cytomegalovirus infection, Cytomegalovirus viraemia, Device related infection, Diarrhoea, Diarrhoea infectious, Diverticular perforation, Diverticulitis, Diverticulitis intestinal haemorrhagic, Empyema, Endocarditis bacterial, Enteritis, Enterococcal bacteraemia, Enterocolitis, Enterocutaneous fistula, Erysipelas, Escherichia sepsis, Eye pain, Facial paralysis, Gastroenteritis, Gastroenteritis salmonella, Gastroenteritis viral, Gastrointestinal candidiasis, Gastrointestinal infection, Genitourinary tract infection, H1N1 influenza, HIV infection, Haematoma infection, Hepatitis infectious mononucleosis, Herpes zoster, Histoplasmosis disseminated, Human herpesvirus 6 infection, Hydrocele, Influenza, Intervertebral discitis, Intestinal obstruction, Intestinal perforation, Intra-abdominal fluid collection, Listeriosis, Liver abscess, Lower respiratory tract infection, Mastitis, Meningitis, Meningitis listeria, Myringitis, Nasal congestion, Necrotising fasciitis, Ophthalmic herpes zoster, Osteomyelitis, Otitis media, Parainfluenzae virus infection, Parotitis, Pelvic abscess, Pelvic inflammatory disease, Pericarditis, Perineal abscess, Periorbital cellulitis, Perirectal abscess, Peritonitis, Pharyngeal abscess, Pharyngolaryngeal abscess, Pneumonia, Pneumonia legionella, Pneumonia mycoplasmal, Pneumonia pneumococcal, Pneumonia staphylococcal, Pneumonia streptococcal, Pneumonia viral, Postoperative abscess, Postoperative wound infection, Procedural intestinal perforation, Proteus infection, Pseudomembranous colitis, Pulmonary oedema, Pulmonary tuberculosis, Pyelonephritis, Pyoderma gangrenosum, Pyrexia, Rash pustular, Rectal abscess, Respiratory tract infection, Respiratory tract infection viral, Salpingitis, Sepsis, Septic shock, Sinusitis, Skin papilloma, Staphylococcal abscess, Staphylococcal infection, Stoma

site abscess, Streptococcal infection, Streptococcal sepsis, Subcutaneous abscess, Tonsillitis, Tooth abscess, Tubo-ovarian abscess, Upper respiratory tract infection, Urinary tract infection, Urinary tract infection bacterial, Urosepsis, Uvulitis, Vaginal abscess, Vascular device infection, Vasculitis, Viral infection, Vulval abscess, Wound abscess, Wound infection staphylococcal.

Malignancy

NMSC PTs: Basal cell carcinoma, Bowen's disease, Penile cancer, Squamous cell carcinoma, and Squamous cell carcinoma of skin.

Malignancy other than NMSC PTs: Adenocarcinoma, Adenocarcinoma of colon, Adenocarcinoma pancreas, B-cell lymphoma, Bladder cancer, Bladder transitional cell carcinoma, Breast cancer, Carcinoid tumour, Cervical dysplasia, Cervix carcinoma stage 0, Chronic lymphocytic leukaemia, Chronic myeloid leukaemia, Clear cell renal cell carcinoma, Colon cancer, Cutaneous T-cell lymphoma, Endometrial adenocarcinoma, Endometrial cancer, Intraocular melanoma, Invasive ductal breast carcinoma, Lentigo maligna, Lobular breast carcinoma in situ, Lymphoma, Malignant melanoma, Malignant melanoma in situ, Oesophageal carcinoma, Oral neoplasm, Ovarian cancer metastatic, Pancreatic carcinoma, Pancreatic carcinoma metastatic, Papillary renal cell carcinoma, Plasma cell myeloma, Prostate cancer, Rectal adenocarcinoma, Renal cancer metastatic, Renal cell carcinoma, Seminoma, Small cell lung cancer, Small intestine adenocarcinoma, Squamous cell carcinoma, Testis cancer, Thyroid cancer, Tongue neoplasm malignant stage unspecified, Transitional cell carcinoma.

Cardiovascular events

Acute coronary syndrome, Acute myocardial infarction, Acute respiratory failure, Angina unstable, Aspiration, Cardiac arrest, Cardiac failure congestive, Cardio-respiratory arrest, Cerebral haemorrhage, Cerebral infarction, Cerebrovascular accident, Congestive cardiomyopathy, Coronary artery disease, Haemorrhagic stroke, Ischaemic cardiomyopathy, Ischaemic stroke, Myocardial infarction, Myocarditis, Pain in extremity, Pulmonary embolism, Sleep apnoea syndrome, Subarachnoid haemorrhage, Sudden death, Ventricular fibrillation.

Serious depression including suicidality

Asphyxia, Carbon monoxide poisoning, Completed suicide, Depression, Overdose, Suicidal ideation, Suicide attempt.

Reversible posterior leukoencephalopathy syndrome

Posterior reversible encephalopathy syndrome.

Venous thromboembolism

Deep vein thrombosis, Embolism venous, May-Thurner syndrome, Portal vein thrombosis, Pulmonary embolism, Retinal vein occlusion, Subclavian vein thrombosis, Thrombophlebitis, Thrombophlebitis superficial.

Exposure During Pregnancy

Abortion, Abortion induced, Abortion spontaneous, Breech delivery, Caesarean section, Complication of pregnancy, Ectopic pregnancy, Exposure during pregnancy, Exposure via body fluid, Paternal exposure during pregnancy, Polyhydramnios, Pre-eclampsia, Pregnancy, Pregnancy of partner, Premature delivery, Premature labour, and Unintended pregnancy.

Annex 8: Summary of Changes to the Risk Management Plan Over Time

Version	Approval Date Procedure	Change
1.6	At the time of authorization 16 January 2009	Safety concerns • Initial presentation of the following important potential risks: 'Serious infections,' 'Malignancy,' 'Cardiovascular events,' 'Serious systemic hypersensitivity reactions,' 'Serious depression,' and 'Exposure during pregnancy.' • Initial presentation of the following missing information: 'Use in pediatrics,' 'Use in patients with hepatic impairment,' 'Use in patients with renal impairment,' 'Use in patients with latent TB or prior history of TB,' 'Use in patients with concurrent malignancy or a history of malignancy,' 'Use after recent vaccination with live bacterial or live viral vaccines,' 'Use in patients with active infections including HIV, hepatitis B, or hepatitis C,' 'Use in patients with recent prior use of other biologic therapy or receiving concomitant immunosuppressive therapy,' 'Use in patients with other forms of psoriasis,' 'Use in patients of different ethnic origins.' Pharmacovigilance Plan None. Risk minimization measures None. Annexes None.
2.0	Line extension – STELARA pre-filled syringe n/a	No major changes noted.
3.0	PSUR 01 (12 December 2008 – 30 June 2009) 17 December 2009	No major changes noted.

Version	Approval Date Procedure	Change
4.0	PSUR 02 (01 July 2009 – 31 December 2009) 24 June 2010	Safety concerns • Elevation of the following important risk from potential to identified: 'Serious systemic hypersensitivity reactions.' • Addition of the following important potential risk: 'Reversible posterior leukoencephalopathy syndrome.' Pharmacovigilance Plan None. Risk minimization measures • Addition of 'Serious systemic hypersensitivity reactions' as a topic to the educational program. Annexes None.
5.0	PSUR 03 (01 January 2010 – 30 June 2010) 18 November 2010	No major changes noted.
6.0	PSUR 04 (01 July 2010 – 31 December 2010) 19 May 2011	No major changes noted.
7.0	EMEA/H/C/000958/II/0018 16 January 2012	Safety concerns • Addition of the following important potential risk: 'Facial palsy.' • Removal of the following missing information: 'Use in patients of different ethnic origins.' Pharmacovigilance Plan None. Risk minimization measures None. Annexes None.
8.0	PSUR 05 and PSUR 06 (01 January 2011 – 31 December 2011) 24 May 2012	No major changes noted.

Version	Approval Date Procedure	Change
9.0	EMEA/H/C/000958/II/029 n/a	Safety concerns • Elevation of the following important risk from potential to identified: 'Facial palsy.' Pharmacovigilance Plan None. Risk minimization measures None. Annexes None. Other • Addition of PsA as a proposed indication.
9.1	EMEA/H/C/000958/II/029 23 July 2013	No major changes noted. Updated the description of the PSOLAR and NDI study populations related to the CHMP's Request for Supplementary Information (RSI) for the proposed PsA indication (EMEA/H/C/000958/II/0029).
10.0	PSUR 07 (January 2012 - 31 December 2012) 11 July 2013	Safety concerns • Addition of the following important identified risk: 'Pustular psoriasis.' • Addition of the following important potential risk: 'Erythrodermic psoriasis.' Pharmacovigilance Plan None. Risk minimization measures None. Annexes None.

Version	Approval Date Procedure	Change
11.0	EMEA/H/C/000958/II/0037 23 January 2014	Safety concerns None. Pharmacovigilance Plan • Removal of the text "Use in patients with renal impairment" as a safety concern addressed for Study C0168Z03 (PSOLAR) because renal insufficiency is not being systematically collected in the PSOLAR registry and was included erroneously in the previous RMPs. Risk minimization measures None. Annexes None. Other • Addition of PsA as an approved indication. • Consolidation of the updates from versions 9.1 and 10.0. • Improvement of lay language for "treatment response" as per Assessment Report for Procedure EMEA/H/C/000958/PSU 006, which included version 10.0.
11.1	EMEA/H/C/000958/II/0041 n/a	Safety concerns • Elevation of the following important risk from potential to identified: Erythrodermic psoriasis. Pharmacovigilance Plan None. Risk minimization measures None. Annexes None.

Version	Approval Date Procedure	Change
11.2	EMEA/H/C/000958/II/0041 23 October 2014	Safety concerns None. Pharmacovigilance Plan None. Risk minimization measures • Update to reflect SmPC wording as requested by PRAC recommendation: – Addition of serious skin conditions, including erythrodermic psoriasis and exfoliative dermatitis to SmPC section 4.4 (Special Warnings and Precautions for Use). – Addition of exfoliative dermatitis and skin exfoliation to SmPC section 4.8 (Undesirable Effects). Annexes None.
12.0	EMEA/H/C/000958/II/0042 n/a	Safety concerns • Modification of missing information from “Use in pediatric patients” to “Use in pediatric patients less than 12 years.” Pharmacovigilance Plan None. Risk minimization measures None. Annexes None.

Version	Approval Date Procedure	Change
12.1	EMEA/H/C/000958/II/0042 n/a	Safety concerns • Addition of the following missing information: Long-term safety in pediatric patients 12 years and older and Long-term impact on growth and development in pediatric patients 12 years and older. None. Pharmacovigilance Plan None. Risk minimization measures None. Annexes None. Other • Consolidation of the updates from versions 11.2 and 12.0.
12.2	EMEA/H/C/000958/II/0042 21 May 2015	Safety concerns None. Pharmacovigilance Plan None. Risk minimization measures None. Annexes None. Other • Update to align with the text on pediatric patients in the final CHMP approved EU SmPC (deletion of 'chronic' in the indication wording and addition of self-administration for adolescents).

Version	Approval Date Procedure	Change
13.0	EMEA/H/C/000958/X/0049/G n/a	Safety concerns • Addition of the following missing information: Long-term safety in adult patients with moderately to severely active CD. • Update of missing information in pediatric patients to include pediatric patients with CD Pharmacovigilance Plan None. Risk minimization measures None. Annexes None. Other • Addition of CD as a proposed indication. • Submission of initial version with dossier for CD submission

Version	Approval Date Procedure	Change
13.1	EMEA/H/C/000958/X/0049/G n/a	Safety concerns None. Pharmacovigilance Plan None. Risk minimization measures None. Annexes None. Other • Update to align text on proposed indication of CD with that in the Day 180 response to EMA during review of MAA for CD • Revision of proposed posology to indicate maintenance dosing every 12 weeks • Addition of sentence to support initial dosing with q8w SC dosing in a sub-group of patients with high burden of disease based on clinical judgment • Revision of pharmaceutical form(s) and strength to indicate "The solution is clear, colorless to light yellow" and to include the concentration for the solution for infusion "130 mg/26 mL (5 mg/mL)" • Update the protocol submission date for the prospective postmarketing observation cohort for CD • Correction of minor error in standardized incidence ratio for malignancy other than non-melanoma skin cancer to 0.96 (95% CI: 0.71-1.26)
13.2	EMEA/H/C/000958/X/0049/G n/a	Safety concerns • Addition of the following important potential risk at the request of the EMA (EMEA/H/C/000958/X/0049): venous thromboembolism Pharmacovigilance Plan None. Risk minimization measures None. Annexes None.

Version	Approval Date Procedure	Change
13.3	EMEA/H/C/000958/X/0049/G n/a 11 November 2016	Safety concerns • Update to align with text in the final CHMP approved EU SmPC update for CD (EMEA/H/C/000958/X/0049) Pharmacovigilance Plan None. Risk minimization measures None. Annexes None.
14.0, Succession 1		General • Update to align with EMA Guidance on the format of the Risk Management Plan (RMP) in the European Union (EU), EMA/PRAC/613102/2015 Rev.2. Safety concerns • Deletion of the following missing information to align with Guidance EMA/PRAC/613102/2015 Rev.2 – 'Use in pediatric patients (except in patients with psoriasis ≥12 years of age)' – 'Use in patients with hepatic impairment' – 'Use in patients with renal impairment' – 'Use after recent vaccination with live bacterial or live viral vaccines' – 'Use in patients with active infections (eg, tuberculosis [TB], HIV, hepatitis B, or hepatitis C)' – 'Use in patients with other forms of psoriasis' – 'Use in patients who have undergone allergy immunotherapy.'

Version	Approval Date Procedure	Change
		Pharmacovigilance Plan • Extension of the protocol for Trial CNTO1275PSO4007 (Pregnancy Research Initiative) to include other indications for ustekinumab as previously agreed with Pharmacovigilance Risk Assessment Committee (PRAC; EMEA/H/C/000958/MEA 024.9). • Update of final report milestone for CNTO1275PSO4005 because the national registries are updated only once per year and the final report will not be available until 1 September 2020 (additional time is needed to prepare the documents required for the Type 2 Variation submission). • Clarification of milestone(s) for the following trials and registries that did not previously include any dates or specific dates: CNTO1275PSO4056, Long-term extension of CNTO1275CRD3003, and RRA-20745. • Removal of Trial CNTO1275PSO3013 (CADMUS JR) from the Pharmacovigilance Plan because this trial is a commitment in the PIP and is not related to a safety concern within the EU-RMP. Risk minimization measures • Removal of Educational Program Annexes • Align with EMA Guidance EMA/PRAC/613102/2015 Rev 2
14.0, Succession 2	EMEA/H/C/000958/IB/0068 24 October 2018	• Final clean document of version 14.0 succession 1 with the QPPV signature.

Version	Approval Date Procedure	Change
15.0, Succession 1	EMEA/H/C/000958/II/0071 Working version, replaced by version 15.0, Succession 3	Safety concerns • Addition of the following missing information: 'Long-term safety in adult patients with moderately to severely active UC.' Pharmacovigilance Plan • Addition of the long-term extension of trial CNTO1275UCO3001 as an additional pharmacovigilance activity to address the safety concern of 'Long-term safety in adult patients with moderately to severely active UC.' Risk minimization measures None. Annexes • Addition of the long-term extension of trial CNTO1275UCO3001 Other • Addition of UC as a proposed indication • Addition of data from completed trial CNTO1275UCO3001 induction and Week 44 data from trial CNTO1275UCO3001 maintenance to clinical trial exposure and risk tables • Update of clinical trial exposure and risk tables from CNTO1275CRD3003 through Week 96 (previously submitted under EMEA/H/C/000958/II/0060). • Update of postauthorization exposure. • Updates were made throughout to align with EMA Guidance on the format of the EU-RMP, EMA/PRAC/613102/2015 Rev.2

Version	Approval Date Procedure	Change
15.0, Succession 2	EMEA/H/C/000958/II/0073 Working version replaced by version 16.1	Safety concerns • Update of the following missing information to amend '12 years' to '6 years': 'Long-term safety in pediatric psoriasis patients 12 years and older'; 'Long-term impact on growth and development in pediatric psoriasis patients 12 years and older'. Pharmacovigilance Plan • Update of Psoriasis Registry CNTO1275PSO4056 (Category 3 pharmacovigilance activity) to reflect the extension of the pediatric psoriasis indication to include children 6 years or older. Risk minimization measures None. Annexes • Update of Psoriasis Registry CNTO1275PSO4056 (Category 3 pharmacovigilance activity) to reflect the extension of the pediatric psoriasis indication to include children 6 years or older. Other • Update of the current indication for pediatric plaque psoriasis to include patients from 6 years and older. • Update of clinical trial exposure tables to include data from ongoing pediatric trial CNTO1275PSO3013. • Update of clinical trial risk tables to include data from pediatric trials CNTO1275PSO3006 and CNTO1275PSO3013 (In the previous RMP, events were only reported in trial CNTO1275PSO3006 for the safety concerns of 'Serious infections' and 'Exposure during pregnancy'; therefore, these events were described in-text only. In the current RMP, since events for the safety concern of 'Serious infections' are reported from trials CNTO1275PSO3006 *and* CNTO1275PSO3013, tabular outputs have been provided.). • Update of postauthorization exposure.

Version	Approval Date Procedure	Change
15.0, Succession 3	EMEA/H/C/000958/II/0071 Working version, replaced by version 15.4	Changes as per version 15.0, Succession 1 with the addition of 2 postauthorization safety studies to describe the safety of ustekinumab and other UC treatments in 2 national cohorts of patients with UC. These studies will address the following: • Important Potential Risks: 'Venous thromboembolism', 'Malignancy', and 'Serious infections (including mycobacterial and salmonella infections)'. • Missing Information: 'Long-term safety in adult patients with moderately to severely active UC'.
15.4	EMEA/H/C/000958/II/0071 Working version replaced by final clean e-signed approved version 15.4	Version containing only changes relating to the addition of the UC indication (as shown in version 15.0, Succession 3). Proposed edits relating to pediatric psoriasis have been removed.
15.4	EMEA/H/C/000958/II/0071 25 July 2019	Final clean approved document containing edits as per version 15.4 (described above). Document contains QPPV e-signature.
16.1	EMEA/H/C/000958/II/0073 Working version replaced by final clean e-signed approved version 16.1	Changes as per version 15.0, Succession 2 with the following additional edits: • Update of the trial design for the Psoriasis Registry CNTO1275PSO4056 (Category 3 pharmacovigilance activity) to reflect that patients will be followed up for 8 years or until the age of 18, whichever occurs first, with corresponding amendment of trial milestones throughout the document. • Update of the Brief Overview of Development to reflect the approval of the indication for the treatment of adult patients with moderately to severely active UC.
16.1	EMEA/H/C/000958/II/0073 Positive opinion: 12 December 2019	Final clean approved document containing edits as per version 16.1 (described above). Document contains QPPV e-signature.

Version	Approval Date Procedure	Change
17.1	EMEA/H/C/000958/IB/0076 Working version replaced by version 17.3.	Final clean approved document containing milestone updates as described below. Document contains QPPV e-signature. • C0168Z03 PSOLAR (milestone updates agreed with EMA on 13 September 2019): – Study completion date changed from 31 December 2020 to 06 September 2021 – Final report submission date changed from 31 August 2021 to 30 June 2022 • Long-term extension of CNTO1275CRD3003 (milestone update agreed with EMA on 18 December 2019): – Final report submission date changed from 30 April 2020 to 31 July 2020 • RRA-20745 (milestones as listed in approved protocol version 5.0, dated 14 May 2019): – Trial start changed from 'to be determined' to 15 January 2018 – Trial finish changed from 'to be determined' to 31 March 2022 – Final report changed from 'to be determined' to 30 September 2022

Version	Approval Date Procedure	Change
17.2	EMEA/H/C/000958/IB/0079 Positive opinion: 25 June 2020	Milestone changes as per version 17.1 for C0168Z03 PSOLAR and the long-term extension of CNTO1275CRD3003. In addition, milestone dates and terminology have been updated for the following additional pharmacovigilance activities: • STELARA UC PASS (SWIBREG and SNDS) and CD PASS RRA-20745: – To align with the current GVP guidance, the wording in Part III.2 has been amended for 'trial start' and 'trial finish'. The new wording is 'start of data collection' and 'end of data collection', respectively. • STELARA UC PASS (SWIBREG and SNDS): – Change of protocol submission date (applies to both studies) from 30 April 2020 to 23 June 2020. – Trial start: 'Not applicable (secondary use of data as of launch of STELARA)' changed to Start of data collection: To be determined. • STELARA CD PASS RRA-20745: – Trial start: 15 January 2018 changed to Start of data collection: 31 December 2019. – Trial finish: 31 March 2022 changed to End of data collection: 30 September 2022. – Final report changed from 30 September 2022 to 30 September 2023.
17.3	EMEA/H/C/000958/IB/0076 Working version replaced by final clean e-signed approved version 17.3	Milestone updates as per version 17.1 for C0168Z03 PSOLAR, the long-term extension of CNTO1275CRD3003, and RRA-20745. In addition, milestones updated for the long-term extension of CNTO1275UCO3001 as agreed with PRAC on 22 April 2020: – Trial finish date changed from 2021 to 31 December 2021. – Final report submission date changed from 2022 to 31 December 2022.
17.3	EMEA/H/C/000958/IB/0076 Positive opinion: 21 April 2020	Final clean approved document containing edits as per version 17.3 (described above). Document contains QPPV e-signature.

Version	Approval Date Procedure	Change
18.1	EMEA/H/C/000958/II/0081/G Working version replaced by version 18.3	Addition of Week 96 data from trial CNTO1275UCO3001 and Week 272 data from trial CNTO1275CRD3003. Safety concerns • No changes. Pharmacovigilance Plan • Removal of long-term extension of Study CNTO1275CRD3003 as an ongoing pharmacovigilance activity. • Removal of 'follow-up of pregnancy reports' as an other form of routine pharmacovigilance activity (Part III.1) as such follow-up is mandatory for all products. Risk minimization measures • Updated routine risk minimization measures to align with the SmPC and GVP guidance. Annexes • Updated to reflect completion of additional pharmacovigilance activity long-term extension of Study CNTO1275CRD3003. Other • Update of clinical trial exposure tables and clinical trial risk tables to include data from trial CNTO1275UCO3001 through Week 96 and trial CNTO1275CRD3003 through Week 272.

Version	Approval Date Procedure	Change
18.2	EMEA/H/C/000958/II/0082 Working version replaced by version 19.1	Completion of the final report for registry study CNTO1275PSO4005 (Nordic Database Initiative). Safety concerns • No changes. Pharmacovigilance Plan • Removal of registry study CNTO1275PSO4005 (Nordic Database Initiative) as an ongoing additional pharmacovigilance activity. Risk minimization measures • No changes. Annexes • Updated to reflect completion of additional pharmacovigilance activity registry study CNTO1275PSO4005 (Nordic Database Initiative). Other • Clarifications to the information included for the important potential risks of 'Reversible posterior leukoencephalopathy syndrome' ('Evidence source(s) and strength of evidence' section) and 'Exposure during pregnancy' ('Evidence source(s) and strength of evidence' and 'Characterization of the risk – Discussion' sections).
18.3	EMEA/H/C/000958/II/0081/G Working version replaced by version 18.4	Updates as per version 18.1 with the following additions: Safety concerns • No changes. Pharmacovigilance Plan • Updates to the study title, objectives, study design and study population of the SWIBREG UC PASS to include patients with CD and use of the Swedish Nationwide Healthcare Registers. • Updates to the UC PASS (SNDS) study title. • Addition of 'Cardiovascular events (MACE only)' to the safety concerns addressed by the UC/CD PASS (Swedish Registers) and the UC PASS (SNDS), category 3 additional pharmacovigilance activities in the pharmacovigilance plan.

Version	Approval Date Procedure	Change
		• Additional safety concern of 'Long term safety in adult patients with moderately to severely active Crohn's disease' added for the UC/CD PASS (Swedish Registers). • Updates to the UC/CD PASS (Swedish Registers) and the UC PASS (SNDS) final report dates. Risk minimization measures • No changes. Annexes • Annex 2: Updated to reflect changes to the UC/CD PASS (Swedish Registers) and the UC PASS (SNDS) in Part III, including: Addition of 'Cardiovascular events (MACE only)' to the safety concerns for UC/CD PASS (Swedish Registers) and the UC PASS (SNDS). Additional safety concern of 'Long term safety in adult patients with moderately to severely active Crohn's disease' added for the UC/CD PASS (Swedish Registers). Addition of protocol references. • Annex 7.3: Clarification of the wording used to describe the review process for cardiovascular events in clinical trials.
18.4	EMEA/H/C/000958/II/0081/G Working version replaced by final clean e-signed approved version 18.4	Version containing only changes relating to Procedure II/0081/G (addition of Week 96 data from Trial CNTO1275UCO3001 and Week 272 data from Trial CNTO1275CRD3003, as shown in version 18.3). Proposed edits relating to Procedure II/0082 (Nordic Database Initiative) have been removed.
18.4	EMEA/H/C/000958/II/0081/G EC decision: 09 March 2021	Final clean HA-approved document containing edits as per version 18.4 (described above). Document contains QPPV e-signature.

Version	Approval Date Procedure	Change
19.1	EMEA/H/C/000958/II/0082 Working version replaced by final clean e-signed approved version 19.1	Version containing only changes relating to Procedure II/0082 (completion of the final report for registry study CNTO1275PSO4005 [Nordic Database Initiative], as shown in version 18.2). Edits relating to Procedure II/0081/G (addition of Week 96 data from Trial CNTO1275UCO3001 and Week 272 data from Trial CNTO1275CRD3003) have been removed. In summary: <u>Safety concerns</u> • No changes. <u>Pharmacovigilance Plan</u> • Removal of registry study CNTO1275PSO4005 (Nordic Database Initiative) as an ongoing additional pharmacovigilance activity. <u>Risk minimization measures</u> • No changes. <u>Annexes</u> • Updated to reflect completion of additional pharmacovigilance activity registry study CNTO1275PSO4005 (Nordic Database Initiative). <u>Other</u> • Clarifications to the information included for the important potential risks of 'Reversible posterior leukoencephalopathy syndrome' ('Evidence source(s) and strength of evidence' section) and 'Exposure during pregnancy' ('Evidence source(s) and strength of evidence' and 'Characterization of the risk – Discussion' sections).
19.1	EMEA/H/C/000958/II/0082 Positive opinion: 11 February 2021	Final clean HA-approved document containing edits as per version 19.1 (described above). Document contains QPPV e-signature.

Version	Approval Date Procedure	Change
20.1	EMEA/H/C/000958/IB/0086 Positive opinion: 05 March 2021 Working version. Approved updates consolidated in version 21.1	Approved edits as per version 19.1 (Procedure II/0082: completion of the final report for registry study CNTO1275PSO4005 [Nordic Database Initiative]) accepted as correct with the following updates relating to the change of milestone date for the submission of the final report for CNTO1275PSO4007 (Pregnancy Research Initiative). In summary: <u>Safety concerns</u> • No changes. <u>Pharmacovigilance Plan</u> • Change of milestone date for the submission of the final report for CNTO1275PSO4007 (Pregnancy Research Initiative) from 01 May 2021 to 01 December 2021. <u>Risk minimization measures</u> • No changes. <u>Annexes</u> • Updated to reflect change of milestone date for the submission of the final report for CNTO1275PSO4007 (Pregnancy Research Initiative) from 01 May 2021 to 01 December 2021.
21.1		Consolidation of updates contained in the following HA-approved EU RMPs: • Version 18.4. Procedure II/0081/G (addition of Week 96 data from Trial CNTO1275UCO3001 and Week 272 data from Trial CNTO1275CRD3003). EC decision: 09 March 2021. • Version 20.1. Procedure IB/0086 (change of milestone date for the submission of the final report for CNTO1275PSO4007 [Pregnancy Research Initiative]). Positive opinion: 05 March 2021.