EU Risk Management Plan
For
Steqeyma
(CT-P43, ustekinumab)

RMP version to be assessed as part of this application:	
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Note: Throughout this document, symbols indicating proprietary names (®, ™) are not displayed. The appearance of product names without these symbols does not imply that these names are not protected.

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List of Abbreviations

Abbreviation/Term	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AZA	Azathioprine
BCG	Bacillus-Calmette-Guérin
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CHMP	Committee for Medicinal Products for Human use
CI	Confidence Interval
CV	Cardiovascular
DMARD	Disease-Modifying Anti-Rheumatic Drug
DNA	Deoxyribonucleic Acid
ECG	Electrocardiographic
EEA	European Economic Area
EMA	European Medicines Agency
EP	Erythrodermic psoriasis
EPAR	European Public Assessment Report
EU	European Union
GVP	Good Pharmacovigilance Practices
HIV	Human Immunodeficiency Virus
HLT	High Level Term
HR	Hazard Ratio
IBD	Inflammatory Bowel Disease
ICH	International Conference for Harmonisation
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
INN	International Non-proprietary Name
IV	Intravenous
mAb	Monoclonal Antibody
MACE	Major Adverse Cardiovascular Event
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MTX	Methotrexate

NMSC	Non-Melanoma Skin Cancer
NTM	Non-TB mycobacterial
NOAEL	No-Observed-Adverse-Effect Level
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OR	Odds Ratio
PFS	Pre-Filled Syringe
PL	Package Leaflet
PsA	Psoriatic arthritis
PT	Preferred Term
PUVA	Psoralen and Ultraviolet A
PY	Patient Year
RMP	Risk Management Plan
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
SC	Subcutaneous
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TB	Tuberculosis
TEAE(s)	Treatment Emergent Adverse Event(s)
TFUQ	Targeted Follow-Up Questionnaire
TNF	Tumour necrosis factor
UC	Ulcerative Colitis
US	United States of America
UVA	Ultraviolet A
UVB	Ultraviolet B
VTE	Venous Thromboembolism

Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Ustekinumab
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, interleukin inhibitors (L04AC05)
Marketing Authorisation Applicant	Celltrion Healthcare Hungary kft.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Steqeyma
Marketing authorisation procedure	Centralised Procedure
Brief description of the product	**Chemical class** Recombinant Deoxyribonucleic Acid (DNA)-derived fully human monoclonal antibody.
	Summary of mode of action Ustekinumab is a fully human immunoglobulin G (IgG)1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells.
	Important information about its composition: Ustekinumab is a fully human IgG1κ monoclonal antibody to interleukin (IL)-12/23 produced in a Chinese Hamster Ovary cell line using recombinant DNA technology.
Hyperlink to the Product Information	Product Information (Section 1.3.1)
Indication(s) in the EEA	Current: Plaque psoriasis Steqeyma is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or psoralen and ultraviolet A (PUVA). Paediatric plaque psoriasis Steqeyma is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

	Psoriatic arthritis (PsA) Steqeyma, alone or in combination with MTX, is indicated for the treatment of active PsA in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Crohn's disease (CD) Steqeyma 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 Tumour necrosis factor (TNFα) antagonist or have medical contraindications to such therapies.
	Proposed: Not applicable
Dosage in the EEA	Current: Plaque psoriasis The recommended posology of Steqeyma is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and 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, and then every 12 weeks thereafter. In these patients, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy. Paediatric plaque psoriasis (6 years and older) The recommended dose of Steqeyma based on body weight is presented in Summary of Product Characteristics (SmPC) Section 4.2 (Posology and Method of Administration). Steqeyma should be administered at Weeks 0 and 4, then every 12 weeks thereafter. There is no dose form for Steqeyma that allows weight-based dosing for paediatric patients below 60 kg. For paediatric plaque psoriasis, Steqeyma is available only as 45 mg and 90 mg solution for injection in pre-filled syringe. Patients weighing less than 60 kg should be accurately dosed on a mg/kg basis using another ustekinumab product for which a 45 mg solution for injection in vial presentation enabling weight-based dosing is available. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment. Psoriatic arthritis The recommended posology of Steqeyma 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.

	Crohn's Disease In the treatment regimen, the first dose of Steqeyma is administered intravenously. For the posology of the intravenous dosing regimen, See Section 4.2 (Posology and Method of Administration) of the Steqeyma 130 mg Concentrate for solution for infusion SmPC. The first subcutaneous administration of 90 mg Steqeyma should take place at week 8 after the IV dose. After this, dosing every 12 weeks is recommended. Patients who have not shown adequate response at 8 weeks after the first subcutaneous dose, may receive a second subcutaneous dose at this time. Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks. Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment. Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit 16 weeks after the IV induction dose or 16 weeks after switching to the 8-weekly maintenance dose.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: For Intravenous (IV) use The solution is clear to slightly opalescent, colourless to pale yellow. Concentrate for solution for infusion: 130 mg/26 mL (5 mg/mL). For Subcutaneous (SC) use The solution is clear to slightly opalescent, colourless to pale yellow. Solution for injection in pre-filled syringe (PFS): 45 mg/0.5 mL and 90 mg/1 mL (90 mg/mL).
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Steqeyma, biosimilar ustekinumab and CT-P43 may be used in this document to describe the investigational product to which this application refers.

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

According to the Guideline on Good Pharmacovigilance Practices (GVP) Module V (EMA/838713/2011 Rev 2) this part of the Risk Management Plan (RMP) is not required for biosimilar medicinal products.

Part II: Module SII - Non-clinical part of the safety specification

Table 2: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies) of CT-P43	Relevance to human usage
Repeat-dose toxicity study of CT-P43: Monkey (Cynomolgus monkey): 3 animals/sex/group, doses of CT-P43 and Stelara at 45 mg/kg SC on days 1, 8, 15 and 22 (Study No. 8416958). All animals survived to their scheduled sacrifice. No CT-P43 or Stelara-related clinical observations, ophthalmic observations, body weight changes, body temperature, respiration rates, blood pressure measurements, electrocardiographic (ECG) measurement, haematology or coagulation parameters, clinical chemistry, urinalysis, organ weights, macroscopic, and microscopic observations were noted for animals administered 45 mg/kg/dose CT-P43 or Stelara.	Stelara has been used in the clinic since 2009. During the repeat-dose toxicity studies, no toxicologically relevant differences were noted in animals treated with CT-P43 or Stelara. Therefore, relevance to human usage was not found. 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).
Placental transfer and excretion into milk **Reproductive/Developmental toxicity of CT-P43** Reproductive toxicology studies comparing CT-P43 and Stelara have not been performed because they are not required according to the European Medicines Agency (EMA) guidance on biosimilar products (Committee for Medicinal Products for Human use [CHMP] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance - non-clinical and clinical issues [EMEA/CHMP/BMWP/42832/2005 Rev1] and Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues [EMA/CHMP/BMWP/403543/2010]). **Reproductive/Developmental toxicity of Stelara** Repeated dose toxicology studies conducted in cynomolgus monkeys showed non 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. 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.	Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development. As a precautionary measure, it is preferable to avoid the use of ustekinumab in pregnancy. Women of childbearing potential should use effective methods of contraception during treatment and for at least 15 weeks after treatment. Nursing mothers should not breast-feed during ustekinumab therapy or up to 15 weeks after treatment.

Key Safety findings (from non-clinical studies) of CT-P43	Relevance to human usage
Genotoxicity/ Carcinogenicity of CT-P43 Genotoxicity/carcinogenicity studies comparing CT-P43 and Stelara have not been performed because they are not required according to the EMA guidance on similar biological medicinal products and monoclonal antibodies (EMEA/CHMP/BMWP/ 42832/2005 Rev1; EMA/CHMP/BMWP/403543/2010). **Genotoxicity/ Carcinogenicity of Stelara** 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 DNA and induce gene mutations, chromosome aberrations and/or DNA damage and is not applicable to biotechnology-derived pharmaceuticals (ICH S6). Carcinogenicity studies were not performed with ustekinumab due to the lack of appropriate models for an antibody with no cross-reactivity to rodent IL-12/23 p40.	Not applicable
General Safety Pharmacology of CT-P43 No specific safety pharmacology studies were performed. Safety endpoints were incorporated into the monkey repeat-dose toxicity study (Study No. 8416958). These endpoints included clinical observations, ECG, blood pressure, and respiration rate. There were no treatment-related changes noted on these parameters. Moreover, no clinical signs or histopathological findings suggestive of central nervous system effects were noted in the 4 week repeat-dose toxicity study in cynomolgus monkeys. This approach is in line with the Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (EMEA/CHMP/BMWP/42832/2005 Rev1) and CHMP Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies (EMA/CHMP/BMWP /403543/2010).	Not applicable
Cardiotoxicity of CT-P43 There was no evidence of cardiotoxicity in the repeat-dose study performed. No non-clinical cardiotoxicity studies have been conducted with CT-P43.	Not applicable

Key Safety findings (from non-clinical studies) of CT-P43	Relevance to human usage
Mechanisms for Drug Interactions of CT-P43 No drug interactions have been studied, although ustekinumab is intended to be given to patients in combination with various other medicinal products.	No interaction studies have been performed in humans.
Juvenile Toxicity Studies of CT-P43 Juvenile toxicity studies were not performed in line with the CHMP EMA guidance on similar biological medicinal products and monoclonal antibodies (EMEA/CHMP/BMWP/ 42832/2005 Rev1) and CHMP guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).	Not applicable

Conclusion on Non-Clinical Data

Non-clinical investigations comparing CT-P43 with the reference product Stelara have not shown them to behave differently from one another in any relevant respects when administered by subcutaneous or IV injection. No unexpected safety findings or signals were identified in the non-clinical programme for CT-P43.

Part II: Module SIII - Clinical trial exposure

The terms Steqeyma and CT-P43 may be used interchangeably in this document.

The clinical development programme for Steqeyma (CT-P43) includes two completed Phase 1 clinical studies in healthy male subjects (Study CT-P43 1.1 and CT-P43 1.2) and one completed Phase 3 study in patients with moderate to severe plaque psoriasis (Study CT-P43 3.1).

- **Study CT-P43 1.1:** A phase 1, 2-part, randomised, double-blind, parallel-group, single-dose study to compare the pharmacokinetics, safety and immunogenicity of three subcutaneous injection formulations of ustekinumab (CT-P43, European Union (EU)-approved Stelara, and United States (US)-licensed Stelara) in healthy male subjects aged between 18 and 55 years of age. Overall, 271 subjects were enrolled and randomly assigned. The first 30 subjects enrolled in Part 1 were randomised (1:1) into 2 treatment groups as follows; Treatment Group 1: CT-P43 (test), 45 mg administered as a single SC injection via pre-filled syringe (PFS), Treatment Group 2: EU-approved Stelara (reference), 45 mg administered as a single SC injection via PFS. Subsequently, 241 subjects enrolled in Part 2 and were randomized (1:1:1) into 3 treatment groups as follows; Treatment Group 1: CT-P43 (test), 45 mg administered as a single SC injection via PFS. Treatment Group 2: EU-approved Stelara (reference), 45 mg administered as a single SC injection via PFS. Treatment Group 3: US-licensed Stelara (reference), 45 mg administered as a single SC injection via PFS. The total study duration for each individual subject who completed the entire study was a maximum of 22 weeks from the date informed consent was signed up to study completion (Day 127/End-of-Study visit).

- **Study CT-P43 1.2:** A phase 1, randomised, double-blind, parallel group, single-dose study to compare the pharmacokinetics, safety, and immunogenicity of three subcutaneous injection formulations of ustekinumab (CT-P43, EU-approved Stelara, and US-licensed Stelara) in healthy Japanese male subjects between 18 and 55 years of age. A total of 325 subjects were administered study drug (111 subjects in the CT- P43 treatment group 108 subjects in the EU-approved Stelara treatment group, and 106 subjects in the US-licensed Stelara treatment group) and 317 subjects in total completed the study (109 subjects in the CT-P43 treatment group, 105 subjects in the EU-approved Stelara treatment group, and 103 subjects in the US-licensed Stelara treatment group). The 3 treatment groups as follows; Treatment Group 1: CT-P43 (test), 45 mg administered as a single SC injection via PFS. Treatment Group 2: EU-approved Stelara (reference), 45 mg administered as a single SC injection via PFS. Treatment Group 3: US-licensed Stelara (reference), 45 mg administered as a single SC injection via PFS. The total study duration for each individual subject who completed the entire study was a maximum of 20 weeks from the date informed consent was signed up to study completion (Day 113/ End-of-Study visit).

- **Study CT-P43 3.1:** A Phase 3, randomised, active-controlled, double-blind study to compare the efficacy and safety of CT-P43 to EU-approved Stelara in patients with moderate to severe plaque psoriasis. A total of 509 patients were randomised and analysed in Treatment Period I and a total of 502 patients were re-randomised at Week 16 and analysed in Treatment Period II. The 2 treatment groups in Treatment Period I are as follows; Treatment Group 1: CT-P43 (test), Treatment Group 2: EU-approved Stelara (reference), 45 mg (who weighed ≤100 kg) or 90 mg (who weighed >100 kg) administered as a SC injection via PFS at Weeks 0 and 4. And the 3 treatment groups in Treatment Period II are as follows; Treatment Group 1: CT-P43 Maintenance (test), Treatment Group 2-1: EU-approved Stelara Maintenance (reference),

Treatment Group 2-2: CT-P43 switched from reference (switched from EU-approved Stelara), 45 mg (who weighed ≤100 kg) or 90 mg (who weighed >100 kg) administered as a SC injection via PFS at Weeks 16, 28 and 40.

Participants in study CT-P43 1.1 and CT-P43 1.2 have not been included in the tables below because this study was conducted in healthy subjects (as opposed to patients), who were exposed to one single dose.

Table 3: Duration of exposure

INDICATION: Plaque psoriasis (CT-P43 3.1)								
Duration of exposure	**CT-P43**						**Ustekinumab reference product ****	
	Total		**CT-P43 only**		**Switched from Ustekinumab reference product***			
	Patients (n)	**Person Time (days)**	**Patients (n)**	**Person Time (days)**	**Patients (n)**	**Person Time (days)**	**Patients (n)**	**Person Time (days)**
Duration < 16 weeks	6	345	4	169	2	176	38	3751
16 weeks ≤ Duration < 40 weeks	164	31482	42	10727	122	20755	113	16149
40 weeks ≤ Duration	210	59537	210	59537	0	0	102	28876
Total	**380**	**91364**	**256**	**70433**	**124**	**20931**	**253**	**48776**

Abbreviation: n=number of patients
**Patients assigned to the switching group switched from reference product to CT-P43 after completion of Treatment Period I.*
***Exposure to reference product during Treatment Period I in the switching group is included in this column.*
Person time (days) = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) or ([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) or ([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1)
The longest duration of exposure is 45.7 weeks.

Table 4: Exposure by Dose

INDICATION: Plaque psoriasis (CT-P43 3.1)								
Dose of exposure	**CT-P43**						**Ustekinumab reference product****	
	Total		**CT-P43 only**		**Switched from Ustekinumab reference product***			
	Patients (n)	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**
Ustekinumab 45mg	295	70583	198	54255	97	16328	199	38341
Ustekinumab 90mg	86	21067	59	16464	27	4603	54	10435
Total	**381*****	**91650**	**257*****	**70719**	**124**	**20931**	**253**	**48776**
Total Cumulative Dose (mg) Mean	272.1	-	271.8	-	272.9	-	268.4	-
Total Cumulative Dose (mg) Median	225	-	225	-	225	-	225	-
Total Cumulative Dose (mg) Min	45	-	45	-	180	-	45	-
Total Cumulative Dose (mg) Max	450	-	450	-	450	-	450	-

Abbreviations: n=number of patients, Min=Minimum, Max=Maximum
**Patients assigned to the switching group switched from reference product to CT-P43 after completion of Treatment Period I.*
***Exposure to reference product during Treatment Period I in the switching group is included in this column.*
****Patients who received multiple strengths (45mg and 90mg) were included in more than one strength, so the total is greater than the number of individual patients.*
Person time (days) = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) or ([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) or ([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1).

Table 5: Exposure by Age and Gender

INDICATION: Plaque psoriasis (CT-P43 3.1)																
Age group (yrs)	**CT-P43**												**Ustekinumab reference product ****			
	Total				**CT-P43 only**				**Switched from Ustekinumab reference product***							
	Patients (n)		**Person Time (days)**		**Patients (n)**		**Person Time (days)**		**Patients (n)**		**Person Time (days)**		**Patients (n)**		**Person Time (days)**	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
18 - 40	127	50	30473	12308	83	37	22987	10105	44	13	7486	2203	89	27	16766	5415
41 - 50	64	37	15081	8851	39	24	11020	6621	25	13	4061	2230	48	27	9103	5408
51 - 64	48	36	12013	8348	36	23	9978	6111	12	13	2035	2237	30	20	6096	3442
≥ 65	5	13	1101	3189	3	11	763	2848	2	2	338	341	6	6	1371	1175
Total	**244**	**136**	**58668**	**32696**	**161**	**95**	**44748**	**25685**	**83**	**41**	**13920**	**7011**	**173**	**80**	**33336**	**15440**

Abbreviations: F = Female; M = Male, n=number of patients
**Patients assigned to the switching group switched from reference product to CT-P43 after completion of Treatment Period I.*
***Exposure to reference product during Treatment Period I in the switching group is included in this column.*
Person time (days) = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1)

Table 6: Exposure by Ethnic Origin

INDICATION: Plaque psoriasis (CT-P43 3.1)								
Race	**CT-P43**						**Ustekinumab reference product****	
	Total		**CT-P43 only**		**Switched from Ustekinumab reference product***			
	Patients (n)	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**
American Indian or Alaska Native	0	0	0	0	0	0	0	0
Asian	36	8220	25	6370	11	1850	23	4062
Black or African American	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0
White	344	83144	231	64063	113	19081	230	44714
Not allowed by Investigator country regulations	0	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	0
Total	**380**	**91364**	**256**	**70433**	**124**	**20931**	**253**	**48776**

Abbreviation: n=number of patients.
**Patients assigned to the switching group switched from reference product to CT-P43 after completion of Treatment Period I.*
***Exposure to reference product during Treatment Period I in the switching group is included in this column.*
Person time (days) = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) or ([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) or ([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1)

Part II: Module SIV - Populations not studied in clinical trials

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

The important exclusion criteria from the pivotal clinical study, CT-P43 3.1, are presented below.

Patient diagnosed with form of psoriasis other than plaque-type such as erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions (e.g., eczema) at the time of the Screening visit that would interfere with evaluations of the effect of the investigational product on psoriasis.

Reason for exclusion: Ustekinumab is not indicated for these forms of psoriasis. In patients with psoriasis, exfoliative dermatitis has been reported following ustekinumab treatment. Patients with plaque psoriasis may develop erythrodermic psoriasis, with symptoms that may be clinically indistinguishable from exfoliative dermatitis, as part of the natural course of their disease. This may confound interpretation of efficacy study endpoints and safety evaluation.

Is it considered to be included as missing information?: No

Rationale: Ustekinumab is not indicated for these forms of psoriasis. Erythrodermic psoriasis, pustular psoriasis are also important identified safety concerns for ustekinumab and are adequately described in the SmPC (Section 4.4 [Special warnings and precautions for use]).

Had shown allergies to the active substance or any of the excipients of ustekinumab or study drug, or patients with a hypersensitivity to immunoglobulin products or natural rubber and latex.

Reason for exclusion: Patients with a history of hypersensitivity to any immunoglobulin product were excluded from the clinical development programme to avoid potentially life-threatening hypersensitivity reactions.

Is it considered to be included as missing information?: No

Rationale: The use of ustekinumab is contraindicated in patients with a known hypersensitivity to the active substance or to any of the excipients. This is adequately described in the SmPC (Section 4.3 [Contraindication] and Section 4.4 [Special warnings and precautions for use]).

Concurrent or past history of infection with human immunodeficiency virus (HIV) or concurrent infection with hepatitis B or hepatitis C. However, a patient with past hepatitis B or C virus infection was allowed if resolved.

Reason for exclusion: Treatment with immunomodulatory agents may increase the risk of infection or worsen an existing infection. Patients with such infections may confound interpretation of efficacy study endpoints and safety evaluation. Moreover, chronic infectious disease may lead to high dropout rates.

Is it considered to be included as missing information?: No

Rationale: Patients with above mentioned conditions were excluded to prevent interference with efficacy and safety study endpoints. Use of ustekinumab is contraindicated in patients with serious

infection. Serious infections are an important potential risk for ustekinumab and adequately described in the SmPC.

Herpes zoster infection within 8 weeks prior to the first administration of the study drug (Day 1).

Concurrent or past history of serious infection requiring hospitalisation or parenteral injection of antibiotics within 8 weeks prior to the first administration of the study drug (Day 1).

Concurrent or past granulomatous infections or other severe or chronic or recurrent infections (such as sepsis, abscess or opportunistic infections, or invasive fungal infections such as histoplasmosis or nontuberculous mycobacterial infection or infected skin wounds or ulcer). However, a patient who had a past diagnosis with sufficient documentation of complete resolution of the infection could be enrolled in the study.

Patient who had concurrent or a history of active tuberculosis (TB). Patient who has a past diagnosis of latent TB unless they have documentation of completing TB prophylaxis, or have received at least the first 3 weeks of country-specific TB prophylaxis prior to the first administration of the study drug (Day 1) and intends to complete its entire course can be enrolled.

Reason for exclusion: Use of ustekinumab is contraindicated in patients with clinically important, active infection. Treatment with immunomodulatory agents may increase the risk of infection or worsen an existing infection. This may confound interpretation of efficacy study endpoints and safety evaluation. Moreover, chronic infectious disease may lead to high dropout rates.

Is it considered to be included as missing information?: Yes (with respect to patients with history of active or latent TB only)

Rationale: Serious infections (including mycobacterial and salmonella infections) are an important potential risk for ustekinumab and the use of ustekinumab is contraindicated in patients with clinically important, active infection such as active TB (SmPC Section 4.3 [Contraindications]) .

Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. Use in patients with a history of tuberculosis is an item of missing information for ustekinumab. In clinical studies, serious bacterial, fungal, and viral infections have been observed in patients receiving ustekinumab.

Caution should be exercised when considering the use of ustekinumab in patients with a chronic infection or a history of recurrent infection or opportunistic infections including reactivation of TB (SmPC Section 4.4 ‘Special warnings and precautions for use’).

Guidance for the management of subjects who develop infections while being treated with ustekinumab is provided in SmPC Section 4.4 [Special Warnings and Precautions for Use].

Female patient who is currently pregnant or breastfeeding, or plans to become pregnant or breastfeed, or male patient who is planning to father a child or donate sperm during study period.

Reason for exclusion: These patients were excluded to minimise risk to pregnant women and nursing mothers and their children. There are no adequate data for the use of ustekinumab in pregnant women, or in males planning to father children.

Is it considered to be included as missing information?: No

Rationale: Exposure during pregnancy is an important potential risk for ustekinumab. SmPC Section 4.6 (Fertility, Pregnancy and Lactation) notes lack of adequate data regarding the use of ustekinumab in pregnant women, advises against its use during pregnancy, and advises for the use of effective methods of contraception during treatment and up to 15 weeks after the end of treatment.

Current or history of any malignancy within the previous 5 years prior to the first administration of the study drug (Day 1) except adequately treated non-metastatic squamous carcinoma of the uterine cervix, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma with no evidence of recurrence for at least 12 weeks prior to the first administration of the study drug (Day 1).

Reason for exclusion: Treatment with an immunomodulatory agent may theoretically increase the risk of developing a malignancy. Concurrent malignancy may complicate the interpretation of efficacy endpoints. Moreover, patients with history of past or concurrent malignancy are prone to frequent hospitalisation, hence higher dropout rates. Malignancy is a potential risk for ustekinumab.

Is it considered to be included as missing information?: No

Rationale: The effects of ustekinumab in patients with malignancies have not been systematically studied. The available data do not allow one to conclude that the risk of treatment of patients with malignancies with ustekinumab is insignificant.

Received a live-attenuated vaccine or Bacillus Calmette-Guérin (BCG) vaccination within 4 weeks prior or within 1 year prior to the first administration of the study drug (Day 1)

Reason for exclusion: The administration of live vaccines during immunomodulatory therapy may increase the risk of active infection following vaccination. Specific studies have not been conducted in patients who had recently received live viral or live bacterial vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving ustekinumab.

Is it considered to be included as missing information?: No

Rationale: Clinical experience suggests the immunosuppression seen with ustekinumab is minimal, this has adequately been described in the SmPC Section 4.4 (Special Warnings and Precautions for Use) that viral or live bacterial vaccines (such as BCG) should not be given concurrently with ustekinumab. Before live viral or live bacterial vaccination, treatment with ustekinumab should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination.

History of organ transplantation, with exception of a corneal transplant, within 12 weeks prior to the first administration of the study drug (Day 1).

Reason for exclusion: Most patients who have undergone organ transplant require immunosuppressant medications that preclude inclusion in clinical trials. Ustekinumab has immunosuppressant properties. The combination may confound the interpretation of both efficacy and safety outcomes in clinical studies.

Is it considered to be included as missing information?: No

Rationale: 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. Concomitant immunosuppressive therapy has adequately been described in SmPC Section 4.4 [Special Warnings and Precautions for Use] and that caution should be exercised when considering concomitant use of other immunosuppressants or when transitioning from other immunosuppressive biologics.

Patient who received or planned to receive prohibited medications (Topical therapies, Ultraviolet A (UVA), Ultraviolet B (UVB), systemic steroids, non-biologic steroids, investigation drug) or treatment that could affect psoriasis.

Reason for exclusion: The safety and efficacy of ustekinumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated in psoriasis. The combination would confound the interpretation of both efficacy and safety outcomes in clinical studies involving psoriasis patients.

Is it considered to be included as missing information?: No

Rationale: Caution should be exercised when considering concomitant use of other treatments for psoriasis and ustekinumab or when transitioning from other treatments. The concern has adequately been described in the SmPC (Section 4.4 [Special warnings and precautions for use] and Section 4.5 [Interaction with other medicinal products and other forms of interaction]).

Patient who had medical conditions such as Diabetes mellitus considered by the investigator to be clinically significant and uncontrolled; Uncontrolled hypertension (as defined by systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥100 mmHg) within the 24 weeks prior to the first administration of the study drug (Day 1); Current or past history of severe uncontrolled cardiac disease or myocardial infarction; Any clinically significant respiratory disease; Any major surgical procedure within 12 weeks prior to the first administration of the study drug (Day 1) or planned during the study; History or evidence of any other clinically significant medical or psychiatric condition.

Patient who has current or chronic inflammatory or autoimmune disease or symptoms other than psoriasis and psoriatic arthritis that might confound study evaluations.

Reason for exclusion: These are precautionary measures applied to clinical trial subjects to reduce the risk of premature discontinuation from the study.

Is it considered to be included as missing information?: No

Rationale: The impracticalities of identifying adequate numbers of patients with progressive concomitant disease in each of these categories precludes the further study of ustekinumab in these patient populations. The risk-benefit balance of the use of ustekinumab should be carefully evaluated on a case-by-case basis in patients with these concomitant diseases. The SmPC of reference product Stelara does not mention any risks associated with use of Stelara specifically in patients with the above-mentioned concomitant diseases.

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

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

Steqeyma has been studied in patients with moderate to severe plaque psoriasis. Up to the data lock point of this RMP, 205 healthy volunteers (80 subjects in the CT-P43 group for Part 2 and 14 subjects in the CT-P43 group for Part 1 in study CT-P43 1.1; 111 subjects in the CT-P43 group in study CT-P43 1.2), and 380 patients with moderate to severe plaque psoriasis (study CT-P43 3.1) have been treated with Steqeyma in the clinical development programme. The treatment duration for patients with moderate to severe plaque psoriasis with Steqeyma was calculated from Treatment Period I, and the longest duration exposure is 45.7 weeks. The median and maximum treatment duration for patients with only CT-P43 were 45.7 weeks and 40.0 weeks respectively.

In addition to the treatment of plaque psoriasis, the reference product Stelara is approved for Paediatric plaque psoriasis, Psoriatic arthritis (PsA), Crohn's disease (CD) and Ulcerative colitis (UC).

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

Table 7: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Paediatric patients	Not included in the clinical development programme of CT-P43.
Elderly patients	Overall, five (5) male and thirteen (13) female patients aged 65 years received CT-P43 in the study CT-P43 3.1 (Table 5). There are limited data available on the use of ustekinumab in patients older than 65 years but there is no evidence that elderly patients have a safety or efficacy profile that differs from younger adult patients.
Pregnant or Breastfeeding women	Pregnant women and nursing mothers were excluded from studies in the clinical development programme. Two cases of pregnancy were reported during CT-P43 3.1 study period in women treated with ustekinumab: One case (2502-0011) had the outcome spontaneous abortion. In the second case (2512-0021), pregnancy was detected after the last study drug administration (i.e. Week 40 dose). The patient was lost to follow-up and outcome of the pregnancy was not reported.
Patients with relevant comorbidities:	

Type of special population	Exposure
Patients with hepatic impairment	Patients with hepatic impairment were not studied in the clinical development programme of CT-P43.
Patients with renal impairment	Patients with renal impairment were not studied in the clinical development programme of CT-P43.
Patients with cardiovascular impairment	Patients with cardiovascular impairment were not included in the clinical development programme of CT-P43.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme of CT-P43.
Immunocompromised patients	Not included in the clinical development programme of CT-P43.
Population with relevant different ethnic origin	Most patients in Study CT-P43 3.1 were Caucasians (White) (Table 6). Ethnic origin is not known to be relevant to the response to treatment with ustekinumab.
Subpopulations carrying relevant genetic polymorphisms	There are no known relevant genetic polymorphisms.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable as the product has not received marketing authorisation yet in any jurisdiction.

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Based on the given mechanism of action of the Steqeyma and its indications, the potential for misuse or abuse for illegal purposes is negligible.

Part II: Module SVII - Identified and potential risks

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

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

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

1. **Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):**

   None.

2. **Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:**

   None.

3. **Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):**

   In accordance with the EU requirements, Steqeyma has been shown to have comparable quality, safety and efficacy to the reference product Stelara. The safety profile of Steqeyma is similar to the reference product Stelara and has been adequately described in the product information.

   The following risks are labelled in the product information for the reference product Stelara and are not important safety concerns for either Stelara or Steqeyma:

   Acne, allergic alveolitis, arthralgia, asthenia, back pain, bullous pemphigoid, cellulitis, cutaneous lupus erythematosus, dental infections, diarrhoea, dizziness, headache, vasculitis, eosinophilic pneumonia, fatigue, injection site erythema, injection site pain, injection site reactions (including haemorrhage, haematoma, induration, swelling and pruritus), lupus-like syndrome, myalgia, nasal congestion, nasopharyngitis, nausea, organising pneumonia, oropharyngeal pain, pruritus, sinusitis, skin exfoliation, viral upper respiratory tract infection, vomiting.

4. **Known risks that do not impact the risk-benefit profile:**

   None.

5. **Other reasons for considering the risks not important:**

   The following risks are labelled in the product information for the reference product Stelara and are not explicitly included in the list of important safety concerns:

Exfoliative dermatitis, herpes zoster, hypersensitivity reactions, upper and lower respiratory tract infection, vulvovaginal mycotic infection.

Exfoliative dermatitis is not included in the list of important safety concerns. However, erythrodermic psoriasis is included in the list as an important identified risk and is usually clinically indistinguishable from exfoliative dermatitis.

Hypersensitivity reactions are not included in the list of important safety concerns unless they are also serious.

Herpes zoster, respiratory tract infection and mycotic infection are not included in the list of important safety concerns unless they are also serious. Serious infections are important potential risks.

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

Important Potential risk: Serious infections (including mycobacterial and salmonella infections)

Risk-benefit impact:

Serious infection is considered an important potential risk with ustekinumab based upon the theoretical risk identified from non-clinical data and in humans who are genetically deficient for the cytokines that are inhibited by ustekinumab (IL-12/23p40 or IL-12Rβ1).

According to the SmPC of the reference product Stelara, and Steqeyma, in the placebo-controlled studies of patients with psoriasis, PsA, CD and UC, serious infection occurred at the rate of 0.03 per patient-year of follow-up in ustekinumab-treated patients (30 serious infections in 930 patient-years of follow-up) and 0.03 in placebo-treated patients (15 serious infections in 434 patient-years of follow-up).

In the controlled and non-controlled periods of psoriasis, PsA, CD and UC clinical studies with the reference product Stelara, the rate of serious infections was 0.02 per patient-year of follow-up in ustekinumab-treated patients (199 serious infections in 11,581 patient-years of follow-up) and serious infections reported included pneumonia, anal abscess, cellulitis, diverticulitis, gastroenteritis and viral infections.

If a serious infection occurs, administration of ustekinumab should be discontinued immediately, until the infection resolves.

The available cumulative information does not provide evidence for an increased risk of serious infections in patients treated with ustekinumab. The benefits of an effective treatment with Steqeyma outweigh the risk of serious infections (including mycobacterial and salmonella infections).

Important Potential risk: Malignancy

Risk-benefit impact:

Immunosuppressants have the potential to increase the risk of malignancy. Some patients who received ustekinumab in clinical studies developed cutaneous and non-cutaneous malignancies.

No studies have been conducted that include patients with a history of malignancy or in patients who develop malignancy and continue treatment with ustekinumab. Thus, caution should be exercised when considering the use of ustekinumab in these patients.

According to the SmPC of the reference product Stelara, and Steqeyma, in the placebo-controlled period of the psoriasis, PsA, CD and UC clinical studies, the incidence of malignancies excluding non-melanoma skin cancer (NMSC) was 0.11 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in 929 patient-years of follow-up) compared with 0.23 for placebo-treated patients (1 patient in 434 patient-years of follow-up).

In the controlled and non-controlled periods of psoriasis, PsA, CD and UC clinical studies with the reference product Stelara, the most frequently observed malignancies, other than NMSC, were prostate, colorectal, and breast cancers, and melanoma. The incidence of NMSC was 0.49 per 100 patient-years of follow-up for ustekinumab-treated patients (56 patients in 11,545 patient-years of follow-up).

Although malignancies have been reported in patients treated with ustekinumab in clinical trials, and in the post marketing setting with the reference product Stelara, available cumulative information does not suggest an increased risk of malignancy in patients treated with ustekinumab. The benefits of an effective treatment with Steqeyma outweigh the risk of malignancy.

Important Potential risk: Cardiovascular events

Risk-benefit impact:

Patients with severe psoriasis are more likely to demonstrate cardiovascular risk factors such as obesity, diabetes, and hypertension when compared with those with no psoriasis, or mild psoriasis (Mehta et al., 2010).

In the controlled Phase 2 and Phase 3 trials in psoriasis with the reference product Stelara, ustekinumab- and placebo-treated patients had a numeric imbalance in investigator reported Major Adverse Cardiovascular Event (MACE) rates, mostly due to a smaller Phase 2 study. Additional analyses were performed and it was concluded that the overall rates of myocardial infarction and stroke with up to 5 years of treatment with ustekinumab in psoriasis patients are comparable with expected rates in either the general population or in the psoriasis population, and are also 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.

Although MACEs have been reported in patients treated with ustekinumab in clinical trials and in the post marketing setting with the reference product Stelara, the available cumulative information does not provide compelling evidence for a significantly increased risk of MACEs in patients treated with ustekinumab. The benefits of an effective treatment with Steqeyma outweigh the apparent risk of cardiovascular events.

Important Potential risk: Serious depression including suicidality

Risk-benefit impact:

Psoriasis can increase the risk for depression and, in rare cases, suicide. Depression has been identified as an adverse drug reaction (ADR) for ustekinumab 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.

According to the SmPC of the reference product Stelara and Steqeyma, the frequency of ustekinumab induced depression is 'Uncommon'.

Cases of serious depression including suicidality are infrequently reported in association with ustekinumab use, and the benefits of an effective treatment with Steqeyma outweigh this risk.

Important Potential risk:Venous thromboembolism

Risk-benefit impact:

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 of 1-8% reported in the inflammatory bowel disease (IBD) literature (Alkim et al., 2017; Danese et al., 2007; Nguyen et al., 2014).

No causal association has been established with the reference product Stelara. The benefits of an effective treatment with Steqeyma outweigh the risk of VTE.

Important Potential risk: Exposure during pregnancy

Risk-benefit impact:

There are no adequate data from the use of ustekinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development. As a precautionary measure, it is preferable to avoid the use of ustekinumab in pregnancy.

According to the SmPC of the reference product Stelara, and Steqeyma, ustekinumab crosses the placenta and has been detected in the serum of infants born to female patients treated with ustekinumab during pregnancy. The clinical impact is unknown; however, the risk of infection in infants exposed in utero to ustekinumab may in theory be increased after birth.

There is no evidence for risk to mother or unborn child for drug exposure during pregnancy.

The benefits of an effective treatment with Steqeyma may outweigh the risk of exposure during pregnancy. The balance of risk and benefit in pregnant women should be assessed on a case by case basis.

Missing information:Long-term safety in paediatric psoriasis patients 6 years and older

Risk-benefit impact:

The safety of reference product Stelara has been studied in two phase 3 studies of paediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks and the second study was in 44 patients from 6 to 11 years of age treated for up to 56 weeks. In general, the adverse events reported in these two studies with safety data up to 1 year were similar to those seen in previous studies in adults with plaque psoriasis.

Ustekinumab has been shown to improve signs and symptoms, and health-related quality of life in paediatric patients 6 years and older with plaque psoriasis.

The benefit of ustekinumab in the indications authorised for the reference product Stelara, is considered to outweigh the risk of long-term use in children aged 6 years and above, an area of missing information that has yet to be characterised.

Missing information:Long-term impact on growth and development in paediatric psoriasis patients 6 years and older

Risk-benefit impact:

The safety of the reference product Stelara has been studied in two phase 3 studies of paediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks and the second study was in 44 patients from 6 to 11 years of age treated for up to 56 weeks. In general, the adverse events reported in these two studies with safety data up to 1 year were similar to those seen in previous studies in adults with plaque psoriasis.

The benefit of ustekinumab in the indications authorised for the reference product Stelara, is considered to outweigh the risk of long-term use in children aged 6 years and above, an area of missing information that has yet to be characterised.

Missing information:Long-term safety in adult patients with moderately to severely active Crohn's disease

Risk-benefit impact:

The safety and efficacy of the reference product Stelara was assessed in three randomised, double-blind, placebo- controlled, multicentre studies in adult patients with moderately to severely active CD (Crohn's Disease Activity Index [CDAI] score of ≥ 220 and ≤ 450). The clinical development programme consisted of two 8-week IV induction studies (UNITI-1 and UNITI-2) followed by a 44-week subcutaneous randomised withdrawal maintenance study (IM-UNITI) representing 52 weeks of therapy. No new safety concerns were identified in this study extension with up to 5 years of treatment in patients with CD.

The benefit of ustekinumab in the indications authorised for the reference product Stelara, is considered to outweigh the risk of long-term use in adults with IBD, an area of missing information that has yet to be characterised.

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

Not applicable as this is an initial RMP.

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

Since Steqeyma is a biosimilar medicine, all risks have been included based on the safety profile of the reference product Stelara, for all indications, Plaque psoriasis, Paediatric plaque psoriasis, PsA, and CD.

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

Important Potential risk: Serious infections (including Mycobacterial and Salmonella Infections)

Medical Dictionary for Regulatory Activities (MedDRA) terms:

SOC: Infections and infestations.

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).

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 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).

Patients with inborn errors of metabolism involving IL-12/23 who have been vaccinated with BCG, have been reported to develop BCG disease (Filipe-Santos et al., 2006). These patients have also been reported to be 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 ustekinumab based upon the theoretical risk identified from nonclinical data and in humans who are genetically deficient for the cytokines that are inhibited by reference product 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 the reference product Stelara is currently unknown.
Across clinical trials in all indications for which the reference product 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.

Characterisation of the risk:

Frequency with 95 % CI for 100 PY:

INDICATION: Plaque psoriasis (CT-P43 3.1)				
	CT-P43			
	Total (N=380)	CT-P43 only (N=256)	Switched from Ustekinumab reference product* (N=124)	Ustekinumab reference product** (N=253)
Total N of TEAEs	3	3	0	3
N of Patients with TEAEs [1] n (%)	3 (0.8%)	3 (1.2%)	0	3 (1.2%)
N of Patients with TEAEs/100PY	1.199	1.556	0.000	2.246
95% CI for N of Patients with TEAEs/100PY	(0.247, 3.505)	(0.321, 4.547)	(0.000, 6.437)	(0.463, 6.565)

Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number; TEAE = Treatment Emergent Adverse Events.
* Patients assigned to the switching group switched from reference product to CT-P43 after completion of Treatment Period I.
** TEAEs occurred during Treatment Period I in the switching group is included in this column.
Patient Year (PY) = ([Date of Last Exposure to Treatment]-[Date of First Exposure to Treatment] + 1) / 365.25 or
[Date of Last Exposure to Treatment] - [Date of First Exposure of Switch] + 1) /365.25 or
(([Date of First Exposure of Switch - 1] - [Date of First Exposure to Treatment] + 1) / 365.25
[1] Includes all subjects who had one or more occurrences of treatment-emergent adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences. From the MedDRA dictionary, version 24.1.

Frequency with Severity, Seriousness and Outcome:

INDICATION: Plaque psoriasis (CT-P43 3.1)				
	CT-P43			
	Total (N=380)	CT-P43 only (N=256)	Switched from Ustekinumab reference product* (N=124)	Ustekinumab reference product** (N=253)
Total N of TEAEs	3	3	0	3
N of Patients with TEAEs [1] n (%)	3 (0.8%)	3 (1.2%)	0	3 (1.2%)
95% CI for Proportion of Patients with TEAEs	(0.16%, 2.29%)	(0.24%, 3.39%)	(0.00%, 2.93%)	(0.25%, 3.43%)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	0	0	0	0
Grade 2	0	0	0	1 (0.4%)
Grade 3	3 (0.8%)	3 (1.2%)	0	2 (0.8%)
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Seriousness [3]				
Serious	3 (0.8%)	3 (1.2%)	0	3 (1.2%)
Non-serious	0	0	0	0
Outcomes [4]				
Missing	0	0	0	0
Recovered	3 (0.8%)	3 (1.2%)	0	3 (1.2%)

INDICATION: Plaque psoriasis (CT-P43 3.1)				
	CT-P43			
	Total (N=380)	CT-P43 only (N=256)	Switched from Ustekinumab reference product* (N=124)	Ustekinumab reference product** (N=253)
Recovering	0	0	0	0
Not recovered	0	0	0	0
Fatal	0	0	0	0

Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number; TEAE = Treatment Emergent Adverse Events.
* Patients assigned to the switching group switched from reference product to CT-P43 after completion of Treatment Period I.
** TEAEs occurred during Treatment Period I in the switching group is included in this column.
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted: Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted: Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted: Outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown + Missing
From the MedDRA dictionary, version 24.1.

Overall, there were six (6) TEAEs related to serious infection (including mycobacterial and salmonella infections); three (3) in the CT-P43 only group (2 cases of COVID-19 pneumonia and 1 case of tooth abscess), none in the switched from reference product group, and three (3) in the reference product group (2 cases of COVID-19 pneumonia and 1 case of COVID-19). The number of patients with TEAEs per 100 patient-years in CT-P43 group was 1.556 (95% CI: 0.321, 4.547), in the switched from reference product group was 0.000 (95% CI: 0.000, 6.437), and in the reference product group was 2.246 (95% CI: 0.463, 6.565).

Of the six TEAEs related to serious infection (including mycobacterial and salmonella infections), all events were serious.

One Grade 2 event and two Grade 3 events were reported in the reference product group. All three events from CT-P43 only group were of Grade 3.

All six TEAEs related to serious infection (including mycobacterial and salmonella infections) were reported as “recovered” at the end of the trial period. The 95% CI for the proportion of patients with TEAEs in the CT-P43 only group was (0.24%, 3.39%), in the switched from reference product group was (0.00%, 2.93%), and in the reference product group was (0.25%, 3.43%).

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 intracellular complex (MAC) disease included male sex (Odds ration [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; IBD; or impaired immunity from acquired immune deficiency syndrome, sickle cell disease, malaria, anti-rejection drugs taken after organ transplants, and corticosteroids).

Preventability:

Ustekinumab 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 ustekinumab 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 ustekinumab should not be administered until the infection resolves.

TB

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

Non-TB mycobacterial infections

Specific recommendations about the prevention of Non-TB mycobacterial infections are not available.

Salmonella

Salmonella infections may result from a variety of sources. Appropriate handling of raw poultry and eggs, avoidance of unpasteurised 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 has a low impact on the benefit-risk balance of ustekinumab considering no causal association has been established with ustekinumab.

Public health impact:

When used according to the recommendations in the product information, including continuous surveillance for serious infections during treatment with ustekinumab, the impact on public health should be minimal.

Important Potential risk: Malignancy

Medical Dictionary for Regulatory Activities (MedDRA) terms:

SMQ: Malignant tumours (narrow).

Potential mechanisms:

Scientific literature suggests that IL-12 can contribute to tumour immunosurveillance (Colombo and Trinchieri, 2002) and exogenous IL-12 can promote tumour-directed cytotoxic T-cell responses in tumour vaccine strategies. In contrast, IL-23 has been reported to promote tumour 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.

Evidence source(s) and strength of evidence:

There is a theoretical risk of malignancy associated with administration of the reference product 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 the reference product Stelara.

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

Characterisation of the risk:

Frequency with 95 % CI for 100 PY:

INDICATION: Plaque psoriasis (CT-P43 3. 1)				
	CT-P43			
	Total (N=380)	**CT-P43 only (N=256)**	**Switched from Ustekinumab reference product* (N=124)**	**Ustekinumab reference product** (N=253)**
Total N of TEAEs	3	3	0	0
N of Patients with TEAEs [1] n (%)	2 (0.5%)	2 (0.8%)	0	0
N of Patients with TEAEs/100PY	0.800	1.037	0.000	0.000
95% CI for N of Patients with TEAEs/100PY	(0.097, 2.888)	(0.126, 3.747)	(0.000, 6.437)	(0.000, 2.762)

Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number; TEAE = Treatment Emergent Adverse Events.
* Patients assigned to the switching group switched from reference product to CT-P43 after completion of Treatment Period I.
** TEAEs occurred during Treatment Period I in the switching group is included in this column.
Patient Year (PY) = ([Date of Last Exposure to Treatment]-[Date of First Exposure to Treatment] + 1) / 365.25 or
[Date of Last Exposure to Treatment] - [Date of First Exposure of Switch] + 1) /365.25 or
(([Date of First Exposure of Switch - 1] - [Date of First Exposure to Treatment] + 1) / 365.25
[1] Includes all subjects who had one or more occurrences of treatment-emergent adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences. From the MedDRA dictionary, version 24.1.

Frequency with Severity, Seriousness and Outcome:

INDICATION: Plaque psoriasis (CT-P43 3.1)				
	CT-P43			
	Total (N=380)	**CT-P43 only (N=256)**	**Switched from Ustekinumab reference product* (N=124)**	**Ustekinumab reference product** (N=253)**
Total N of TEAEs	3	3	0	0
N of Patients with TEAEs [1] n (%)	2 (0.5%)	2 (0.8%)	0	0
95% CI for Proportion of Patients with TEAEs	(0.06%, 1.89%)	(0.09%, 2.79%)	(0.00%, 2.93%)	(0.00%, 1.45%)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	1 (0.3%)	1 (0.4%)	0	0
Grade 2	0	0	0	0
Grade 3	1 (0.3%)	1 (0.4%)	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Seriousness [3]				
Serious	1 (0.3%)	1 (0.4%)	0	0
Non-serious	1 (0.3%)	1 (0.4%)	0	0
Outcomes [4]				

INDICATION: Plaque psoriasis (CT-P43 3.1)				
	CT-P43			
	Total (N=380)	CT-P43 only (N=256)	Switched from Ustekinumab reference product* (N=124)	Ustekinumab reference product** (N=253)
Missing	0	0	0	0
Recovered	0	0	0	0
Recovering	1 (0.3%)	1 (0.4%)	0	0
Not recovered	1 (0.3%)	1 (0.4%)	0	0
Fatal	0	0	0	0

Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number; TEAE = Treatment Emergent Adverse Events.
* Patients assigned to the switching group switched from reference product to CT-P43 after completion of Treatment Period I.
** TEAEs occurred during Treatment Period I in the switching group is included in this column.
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted: Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted: Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted: Outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown + Missing
From the MedDRA dictionary, version 24.1.

Overall, there were three (3) TEAEs in two (2) patients related to malignancy (neoplasm, adrenal neoplasm, tubular breast carcinoma); all three (3) events were in the CT-P43 only group. The number of patients with TEAEs per 100 patient-years in CT-P43 group was 1.037 (95% CI: 0.126, 3.747), in the switched from reference product group it was 0.000 (95% CI: 0.000, 6.437), and in the reference product group it was 0.000 (95% CI: 0.000, 2.762).

Of the two patients, one patient (0.4%), was categorised as having a serious event, and one patient (0.4%) was categorised as having two non-serious events.

One of the patients had two Grade 1 events (neoplasm and adrenal neoplasm), and the other patient had Grade 3 event (tubular breast carcinoma) in the CT-P43 only group. Of these, only Grade 3 of tubular breast carcinoma was classified as malignancy after medical review.

One TEAE each related to malignancy was reported as “recovering” and “not recovered” simultaneously at the end of the trial period. The 95% CI for the proportion of patients with TEAEs in the CT-P43 only group was (0.09%, 2.79%), in the switched from reference product group was (0.00%, 2.93%), and in the reference product group was (0.00%, 1.45%).

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 cancer include increasing age, lifestyle factors (such as use of alcohol and tobacco, sun exposure, 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 ultraviolet 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 ustekinumab in patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy, or those with a history of PUVA treatment, should be monitored for the appearance of non-melanoma skin cancer (SmPC Section 4.4 [Special Warnings and Precautions of Use]).

Impact on the risk-benefit balance of the product:

Although malignancies have been reported in patients treated with ustekinumab in both clinical trials and in the post marketing setting with the reference product Stelara, available cumulative information does not suggest an increased risk of malignancy in patients treated with ustekinumab. This safety concern has a low impact on the benefit-risk balance of ustekinumab considering no causal association has been established with ustekinumab.

Public health impact:

When used according to the recommendations in the product information, the impact on public health should be minimal.

Important Potential risk: Cardiovascular events

Medical Dictionary for Regulatory Activities (MedDRA) terms:

SOC: Cardiac disorders.

Potential mechanisms:

Patients with severe psoriasis are more likely to demonstrate cardiovascular (CV) risk factors such as obesity, diabetes, and hypertension when compared with those with no psoriasis, 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 cardiovascular (CV) events in subjects on anti-IL-12/23p40 therapy such as with the reference product 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, of the reference product Stelara in psoriasis, resulting predominantly from an imbalance in event rates from a smaller Phase 2 trial. Additional analyses performed internally by the Marketing Authorisation Holder (MAH) of reference product Stelara show that the overall rates of myocardial infarction and stroke with up to 5 years of treatment with the reference product 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.

Characterisation of the risk:

Frequency with 95 % CI for 100 PY:

INDICATION: Plaque psoriasis (CT-P43 3.1)				
	CT-P43			**Ustekinumab reference product** (N=253)**
	Total (N=380)	**CT-P43 only (N=256)**	**Switched from Ustekinumab reference product* (N=124)**	
Total N of TEAEs	1	1	0	0
N of Patients with TEAEs [1] n (%)	1 (0.3%)	1 (0.4%)	0	0
N of Patients with TEAEs/100PY	0.400	0.519	0.000	0.000
95% CI for N of Patients with TEAEs/100PY	(0.010, 2.227)	(0.013, 2.889)	(0.000, 6.437)	(0.000, 2.762)

Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number; TEAE = Treatment Emergent Adverse Events.
* Patients assigned to the switching group switched from reference product to CT-P43 after completion of Treatment Period I.
** TEAEs occurred during Treatment Period I in the switching group is included in this column.
Patient Year (PY) = ([Date of Last Exposure to Treatment]-[Date of First Exposure to Treatment] + 1) / 365.25 or
[Date of Last Exposure to Treatment] - [Date of First Exposure of Switch] + 1) /365.25 or
(([Date of First Exposure of Switch - 1] - [Date of First Exposure to Treatment] + 1) / 365.25
[1] Includes all subjects who had one or more occurrences of treatment-emergent adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences. From the MedDRA dictionary, version 24.1.

Frequency with Severity, Seriousness and Outcome:

INDICATION: Plaque psoriasis (CT-P43 3.1)				
	CT-P43			Ustekinumab reference product** (N=253)
	Total (N=380)	CT-P43 only (N=256)	Switched from Ustekinumab reference product* (N=124)	
Total N of TEAEs	1	1	0	0
N of Patients with TEAEs [1] n (%)	1 (0.3%)	1 (0.4%)	0	0
95% CI for Proportion of Patients with TEAEs	(0.01%, 1.46%)	(0.01%, 2.16%)	(0.00%, 2.93%)	(0.00%, 1.45%)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	0	0	0	0
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	1 (0.3%)	1 (0.4%)	0	0
Seriousness [3]				
Serious	1 (0.3%)	1 (0.4%)	0	0
Non-serious	0	0	0	0
Outcomes [4]				
Missing	0	0	0	0
Recovered	0	0	0	0
Recovering	0	0	0	0
Not recovered	0	0	0	0
Fatal	1 (0.3%)	1 (0.4%)	0	0

Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number; TEAE = Treatment Emergent Adverse Events.
* Patients assigned to the switching group switched from reference product to CT-P43 after completion of Treatment Period I.
** TEAEs occurred during Treatment Period I in the switching group is included in this column.
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted: Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted: Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted: Outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown + Missing
From the MedDRA dictionary, version 24.1.

Overall, there was one (1) TEAE of myocardial infarction related to CV events in the CT-P43 only group. The number of patients with TEAEs per 100 patient-years in CT-P43 group was 0.519 (95% CI: 0.013, 2.889), in the switched from reference product group it was 0.000 (95% CI: 0.000, 6.437), and in the reference product group it was 0.000 (95% CI: 0.000, 2.762).

The one event (0.4%) in the CT-P43 group was categorised as a serious event. One event reported in the CT-P43 only group was categorised as Grade 5 event and the reported outcome was “fatal”.

The 95% CI for the proportion of patients with TEAEs in the CT-P43 only group was (0.01%, 2.16%), in the switched from reference product group was (0.00%, 2.93%), and in the reference product group was (0.00%, 1.45%).

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.

Preventability:

The prevention of cardiovascular disease relies on modifying known risk factors. There is currently no established relationship between cardiovascular events and ustekinumab. The impact of ustekinumab on risk factors for cardiovascular disease, such as hypertension, diabetes, glycaemic control, and weight was evaluated in Phase 3 trials for psoriasis and PsA, and no apparent impact was found.

Impact on the risk-benefit balance of the product:

While there have been reports of MACEs in patients treated with ustekinumab in both clinical trials and post-marketing studies with the reference product Stelara, the available data do not provide conclusive evidence of an increased risk of MACEs in patients treated with ustekinumab. Therefore, the risk-benefit balance of the product is not significantly impacted.

Public health impact:

When used according to the recommendations in the product information, the impact on public health should be minimal.

Important Potential risk: Serious depression including suicidality

Medical Dictionary for Regulatory Activities (MedDRA) terms:

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

Potential mechanisms:

The potential mechanism of depression due to ustekinumab is not understood. However, it has been suggested that the inflammatory response in psoriasis and other autoimmune disorders may contribute to the development of depression, and thus, the use of ustekinumab as an anti-inflammatory medication may indirectly affect the risk of depression (Sahi et al., 2020).

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 and Steqeyma (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 of the reference product Stelara. The incidence of serious depression including suicidality across indications remains low. One (0.3%) TEAE related to serious depression including suicidality was reported in the CT-P43 only group from the Steqeyma clinical trial CT-P43 3.1.

The available safety data from both clinical studies and post marketing experience with the reference product Stelara 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 ustekinumab.

Characterisation of the risk:

Frequency with 95 % CI for 100 PY:

INDICATION: Plaque psoriasis (CT-P43 3.1)				
	CT-P43			
	Total (N=380)	**CT-P43 only (N=256)**	**Switched from Ustekinumab reference product* (N=124)**	**Ustekinumab reference product** (N=253)**
Total N of TEAEs	1	1	0	0
N of Patients with TEAEs [1] n (%)	1 (0.3%)	1 (0.4%)	0	0
N of Patients with TEAEs/100PY	0.400	0.519	0.000	0.000
95% CI for N of Patients with TEAEs/100PY	(0.010, 2.227)	(0.013, 2.889)	(0.000, 6.437)	(0.000, 2.762)

Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number; TEAE = Treatment Emergent Adverse Events.
* Patients assigned to the switching group switched from reference product to CT-P43 after completion of Treatment Period I.
** TEAEs occurred during Treatment Period I in the switching group is included in this column.
Patient Year (PY) = ([Date of Last Exposure to Treatment]-[Date of First Exposure to Treatment] + 1) / 365.25 or
[Date of Last Exposure to Treatment] - [Date of First Exposure of Switch] + 1) /365.25 or
(([Date of First Exposure of Switch - 1] - [Date of First Exposure to Treatment] + 1) / 365.25
[1] Includes all subjects who had one or more occurrences of treatment-emergent adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences. From the MedDRA dictionary, version 24.1.

Frequency with Severity, Seriousness and Outcome:

INDICATION: Plaque psoriasis (CT-P43 3.1)				
	CT-P43			
	Total (N=380)	**CT-P43 only (N=256)**	**Switched from Ustekinumab reference product* (N=124)**	**Ustekinumab reference product** (N=253)**
Total N of TEAEs	1	1	0	0
N of Patients with TEAEs [1] n (%)	1 (0.3%)	1 (0.4%)	0	0
95% CI for Proportion of Patients with TEAEs	(0.01%, 1.46%)	(0.01%, 2.16%)	(0.00%, 2.93%)	(0.00%, 1.45%)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	0	0	0	0
Grade 2	0	0	0	0
Grade 3	1 (0.3%)	1 (0.4%)	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Seriousness [3]				

INDICATION: Plaque psoriasis (CT-P43 3.1)				
	CT-P43			Ustekinumab reference product** (N=253)
	Total (N=380)	CT-P43 only (N=256)	Switched from Ustekinumab reference product* (N=124)	
Serious	1 (0.3%)	1 (0.4%)	0	0
Non-serious	0	0	0	0
Outcomes [4]				
Missing	0	0	0	0
Recovered	0	0	0	0
Recovering	0	0	0	0
Not recovered	1 (0.3%)	1 (0.4%)	0	0
Fatal	0	0	0	0

Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number; TEAE = Treatment Emergent Adverse Events.
* Patients assigned to the switching group switched from reference product to CT-P43 after completion of Treatment Period I.
** TEAEs occurred during Treatment Period I in the switching group is included in this column.
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted: Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted: Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted: Outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown + Missing
From the MedDRA dictionary, version 24.1.

Overall, there was one (1) TEAEs related to serious depression including suicidality, in the CT-P43 only group. The number of patients with TEAEs per 100 patient-years in CT-P43 group was 0.519 (95% CI: 0.013, 2.889), in the switched from reference product group it was 0.000 (95% CI: 0.000, 6.437), and in the reference product group it was 0.000 (95% CI: 0.000, 2.762).

This one event (0.4%) in the CT-P43 group was categorised as a serious event.

One event reported in the CT-P43 only group was categorised as Grade 3 event and the reported outcome was “Not recovered”.

The 95% CI for the proportion of patients with TEAEs in the CT-P43 only group was (0.01%, 2.16%), in the switched from reference product group was (0.00%, 2.93%), and in the reference product group was (0.00%, 1.45%).

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.

Preventability:

There is no known means of preventing depression.

Impact on the risk-benefit balance of the product:

In both clinical trials and post marketing reports of the reference product Stelara, depression has been reported in patients treated with ustekinumab. However, based on available cumulative information, there is no evidence for an increased risk of depression associated with the use of ustekinumab. Therefore, the product's risk-benefit balance does not appear to be significantly impacted.

Public health impact:

When used according to the recommendations in the product information, the impact on public health should be minimal.

Important Potential risk: Venous thromboembolism

Medical Dictionary for Regulatory Activities (MedDRA) terms:

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

Potential mechanisms:

The exact mechanism of VTE due to ustekinumab is not understood, but it is thought to be related to its immunomodulatory effects. Ustekinumab works by binding to and inhibiting the activity of interleukin-12 (IL-12) and interleukin-23 (IL-23), two cytokines that play a role in inflammation and the immune response.

One proposed mechanism for VTE with ustekinumab is through its effects on the clotting system. IL-12 and IL-23 have been shown to promote the activation of platelets and the coagulation cascade, which can increase the risk of blood clots. By inhibiting these cytokines, ustekinumab may reduce platelet activation and decrease clotting activity, potentially increasing the risk of VTE (Papa et al., 2020).

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 immobilisation, hospitalisation, surgical interventions, oral contraceptive use, etc.).
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 the reference product 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 post marketing data with the reference product Stelara, do not indicate an increased rate with ustekinumab treatment.

Characterisation of the risk:

There were no TEAEs reported for VTE in the CT-P43 only group (256 patients), switched from reference product group (124 patients), and the reference product group (253 patients) in Study CT-P43 3.1.

The number of patients with TEAEs per 100 patient-years was 0.000 (95% CI: 0.000, 1.913) in the CT-P43 only group, 0.000 (95% CI: 0.000, 6.437) in switched from reference product group, and 0.000 (95% CI: 0.000, 2.762) in the reference product group.

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.

Preventability:

Patients with risk factors for venous thrombosis may require prophylactic anticoagulation. Prevention is also aimed at reducing acquired risk factors through appropriate measures like providing adequate hydration, effective anti-inflammatory treatment, early mobilisation 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 post marketing setting with the reference product Stelara, 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.

Public health impact:

When used according to the recommendations in the product information, the impact on public health should be minimal.

Important Potential risk: Exposure during pregnancy

Medical Dictionary for Regulatory Activities (MedDRA) terms:

PT: Exposure during pregnancy

Potential mechanisms:

Ustekinumab can cross the placenta and reach the developing foetus during pregnancy.

One potential mechanism of exposure during pregnancy by ustekinumab is through the placenta. Ustekinumab can bind to the placental Fc receptor and cross the placenta to reach the developing foetus. Once in the foetus, ustekinumab can interact with its target molecules, potentially leading to adverse effects on foetal development (Mitrova et al., 2021).

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/foetal 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 non-clinical investigations on this topic and the limited data in humans related to exposure during pregnancy.

Characterisation of the risk:

There were no TEAEs reported for exposure during pregnancy in the CT-P43 only group (256 patients), switched from reference product group (124 patients), and the reference product group (253 patients) in Study CT-P43 3.1.

The number of patients with TEAEs per 100 patient-years was 0.000 (95% CI: 0.000, 1.913) in the CT-P43 only group, 0.000 (95% CI: 0.000, 6.437) in switched from reference product group, and 0.000 (95% CI: 0.000, 2.762) in the reference product group.

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 foetus and are recommended to be avoided during pregnancy.

A recent update on the safety of IBD medications in pregnancy summarised 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.

Preventability:

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]).

Impact on the risk-benefit balance of the product:

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

Public health impact:

When used according to the recommendations in the product information, the impact on public health should be minimal.

SVII.3.2. Presentation of the missing information

Long-term safety in paediatric psoriasis patients 6 years and older

Evidence source:

Clinical trials for the reference product Stelara (Trial CNTO1275PSO3006 and the main study for trial CNTO1275PSO3013) investigated the use of ustekinumab in paediatric psoriasis patients 6 years and older through 60 weeks and 56 weeks, respectively.

Population in need of further characterisation:

Paediatric patients with psoriasis ≥6 years of age with long-term exposure to ustekinumab.

Long-term impact on growth and development in paediatric psoriasis patients 6 years and older

Evidence source:

Clinical trials for the reference product Stelara (Trial CNTO1275PSO3006 and the main study for trial CNTO1275PSO3013) investigated the use of ustekinumab in paediatric psoriasis patients 6 years and older through 60 weeks and 56 weeks, respectively.

Population in need of further characterisation:

Paediatric patients with psoriasis ≥6 years of age with long-term exposure to ustekinumab.

Long-term safety in adult patients with moderately to severely active Crohn's disease

Evidence source:

Clinical trials for the reference product Stelara (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 characterisation:

Adults with moderately to severely active CD who have been treated with ustekinumab beyond maintenance Week 272.

Part II: Module SVIII - Summary of the safety concerns

Table 8: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Serious infections (including mycobacterial and salmonella infections) • Malignancy • Cardiovascular events • Serious depression including suicidality • Venous thromboembolism • Exposure during pregnancy
Missing information	• Long-term safety in paediatric psoriasis patients 6 years and older • Long-term impact on growth and development in paediatric psoriasis patients 6 years and older • Long-term safety in adult patients with moderately to severely active Crohn's disease

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond collecting Individual Case Safety Report (ISCR) including the brand name and batch number, adverse reactions reporting and signal detection:

Specific Adverse Reaction Follow-up Questionnaires	
Safety Concern	**Purpose/Description**
Serious infections (including mycobacterial and salmonella infections)	Topic of interest (TOI) targeted follow-up questionnaire (TFUQ) to collect information on serious infections and opportunistic infections and TOI TFUQ to collect information on tuberculosis
Malignancy	TOI TFUQ to collect information on malignancies (including lymphoma, second and secondary malignancies)
Cardiovascular events	TOI TFUQ to collect information on cardiovascular events
Venous thromboembolism	TOI TFUQ to collect information on venous thromboembolism

Other forms of routine pharmacovigilance activities:

None.

III.2 Additional pharmacovigilance activities

Not applicable as there are no additional pharmacovigilance activities planned for Steqeyma.

III.3 Summary Table of additional Pharmacovigilance activities

Table 9: Part III.1: On-going and planned additional pharmacovigilance activities

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

Part IV: Plans for Post-authorisation Efficacy Studies

Not applicable, since there are no post authorisation efficacy studies planned for Steqeyma.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Safety concern	Routine risk minimisation activities
Serious infections (including mycobacterial and salmonella infections) (Important potential risk)	Routine risk communication: SmPC Sections 4.3, 4.4, 4.5, 4.6, and 4.8 PL Sections- 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.4 (Special Warnings and Precautions for Use) • Guidance regarding evaluation of patients for TB infection, treatment of latent TB, and administration of anti-TB therapy in patients with a history of latent or active TB prior to initiation of Steqeyma. • Recommendation to monitor patients for signs and symptoms of active TB during and after steqeyma treatment. • Guidance for managing patients who develop a serious infection. • Recommendations regarding the administration of live vaccines to patients receiving ustekinumab and to infants exposed to ustekinumab in utero. (The same recommendations are included in SmPC section 4.5 [Interaction with Other Medicinal Products and Other Forms of Interaction]). SmPC section 4.6 (Fertility, Pregnancy and Lactation) • Recommendation regarding the administration of live vaccines to infants exposed to ustekinumab in utero. PL section 2 • Guidance for patients who have recently had or are going to have a vaccination. • Guidance for mothers who received ustekinumab while pregnant and recommendation regarding the administration of live vaccines to infants exposed to ustekinumab in utero. • Guidance for patients who have had a recent infection, have any abnormal skin openings (fistulae), are over 65 years of age, or have recently been exposed to someone who might have TB. PL section 4 • Guidance for patients who develop signs of an infection or have open cuts or sores while using steqeyma. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.*
Malignancy (Important potential risk)	Routine risk communication: SmPC Sections 4.4 and 4.8 PL Section- 2

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance is given for the patients in SmPC Section 4.4, the patients greater than 60 years of age, patients with medical history of prolonged immunosuppresant therapy or PUVA treatment should be monitored for NMSC. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.*
Cardiovascular Events (Important potential risk)	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.*
Serious depression including suicidality (Important potential risk)	Routine risk communication: SmPC Section 4.8 PL Section- 4 *Serious depression including suicidality is not specifically mentioned in the SmPC and is added as per the reference drug RMP.* Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.*
Venous Thromboembolism (Important potential risk)	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.*
Exposure during Pregnancy	Routine risk communication: SmPC Section 4.6 PL Section- 2

Safety concern	Routine risk minimisation activities
(Important potential risk)	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance is given in the SmPC Section 4.6 that as a precautionary measure, it is preferable to avoid the use of Steqeyma in pregnancy and women of childbearing potential should use effective methods of contraception during treatment and for at least 15 weeks after treatment. • Advice for patients who become pregnant, think that they may be pregnant, or are planning to become pregnant while using Steqeyma (PL section 2) Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.*
Long-term safety in paediatric psoriasis patients 6 years and older (Missing information)	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication*
Long-term impact on growth and development in paediatric psoriasis patients 6 years and older (Missing information)	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine *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 (Missing information)	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.*

V.2. Additional Risk Minimisation Measures

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

V.3 Summary of risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious infections (including mycobacterial and salmonella infections) (Important potential risk)	Routine risk minimisation measures: • *SmPC Sections 4.3, 4.5, 4.6 and 4.8* • *SmPC Section 4.4 where guidance and management of serious infections are included.* • *PL Sections- 2 and 4* Legal status: *Prescription only medicine* *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Adverse reaction follow-up Questionnaire Additional pharmacovigilance activities: None
Malignancy (Important potential risk)	Routine risk minimisation measures: • *SmPC Section 4.8* • *Guidance is given for the prescribers in SmPC Section 4.4, the patients greater than 60 years of age, patients with medical history of prolonged immunosuppresant therapy or PUVA treatment should be monitored for NMSC.* • *PL Section- 2* Legal status: *Prescription only medicine* *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Adverse reaction follow-up Questionnaire Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cardiovascular Events (Important potential risk)	Routine risk minimisation measures: None Legal status: *Prescription only medicine* *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Adverse reaction follow-up Questionnaire Additional pharmacovigilance activities: None
Serious depression including suicidality (Important potential risk)	Routine risk minimisation measures: • *SmPC Section 4.8* • *PL Section- 4* Legal status: *Prescription only medicine* *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Venous Thromboembolism (Important potential risk)	Routine risk minimisation measures: None Legal status: *Prescription only medicine* *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Adverse reaction follow-up Questionnaire Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Exposure during Pregnancy (Important potential risk)	Routine risk minimisation measures: • *Guidance is given in the SmPC Section 4.6 to avoid the use of Steqeyma in pregnancy and use of effective methods of contraception are recommended during and 15 weeks after treatment.* • *PL Section- 2* Legal status: *Prescription only medicine* *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Long-term safety in paediatric psoriasis patients 6 years and older (Missing information)	Routine risk minimisation measures: None Legal status: *Prescription only medicine* *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Long-term impact on growth and development in paediatric psoriasis patients 6 years and older (Missing information)	Routine risk minimisation measures: None Legal status: *Prescription only medicine* *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term safety in adult patients with moderately to severely active Crohn's disease (Missing information)	Routine risk minimisation measures: None Legal status: *Prescription only medicine* *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Part VI: Summary of the risk management plan

Summary of risk management plan for Steqeyma (ustekinumab biosimilar)

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

Steqeyma's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Steqeyma should be used and how the risks can be managed.

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

I. The medicine and what it is used for

Steqeyma is authorised for plaque psoriasis, paediatric plaque psoriasis, psoriatic arthritis (PsA), and Crohn's disease (CD) (see SmPC of Steqeyma 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 Steqeyma's benefits can be found in Steqeyma'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/steqeyma*.

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

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

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

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

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment - so that

immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

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

List of important risks and missing information	
Important identified risks	None
Important potential risks	• Serious infections (including mycobacterial and salmonella infections) • Malignancy • Cardiovascular events • Serious depression including suicidality • Venous thromboembolism • Exposure during pregnancy
Missing information	• Long-term safety in paediatric psoriasis patients 6 years and older • Long-term impact on growth and development in paediatric psoriasis patients 6 years and older • Long-term safety in adult patients with moderately to severely active Crohn’s disease

II.B Summary of important risks

Important Potential risk: Serious infections (including mycobacterial and salmonella infections)	
Evidence for linking the risk to 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 ustekinumab based upon the theoretical risk identified from nonclinical data and in humans who are genetically deficient for the cytokines that are inhibited by reference product 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 the reference product Stelara is currently unknown. Across clinical trials in all indications for which the reference product 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 intracellular 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 disease [IBD]; or impaired immunity from acquired immune deficiency syndrome, sickle cell disease, malaria, anti-rejection drugs taken after organ transplants, and corticosteroids).
Risk minimisation measures	Routine risk minimisation measures: • *SmPC Sections 4.3, 4.5, 4.6 and 4.8* • *SmPC Section 4.4 where guidance and management of serious infections are included.* • *PL Sections- 2 and 4* Legal status: *Prescription only medicine* *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.* Additional risk minimisation measures: None
Important Potential risk: Malignancy	
Evidence for linking the risk to medicine	There is a theoretical risk of malignancy associated with administration of the reference product 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 the reference product Stelara. Long-term effects of the reference product Stelara on existing malignancies or in patients with a history of malignancy are not known. In light of the theoretic risk and the longer latency period for the development of malignancy, the topic warrants continued surveillance and malignancy is considered an important potential risk.
Risk factors and risk groups	Among psoriasis patients, increased risk of solid cancers appears to be related to alcohol drinking and cigarette smoking. In addition, exposure to PUVA and immunosuppressants, including cyclosporin and possibly Methotrexate (MTX), has been associated with squamous cell carcinoma in psoriasis patients. General risk factors for cancer include increasing age, lifestyle factors (such as use of

	alcohol and tobacco, sun exposure, and obesity), family history of cancer, and certain environmental exposures. Risk factors for the development of malignancy can differ by cancer site. However, in general, factors that can increase risk of malignancies in IBD patients include but are not limited to smoking, ongoing inflammation, and carcinogenic effects of immunosuppressive drugs.
Risk minimisation measures	Routine risk minimisation measures: • *SmPC Section 4.8* • *Guidance is given for the prescribers in SmPC Section 4.4, the patients greater than 60 years of age, patients with medical history of prolonged immunosuppresant therapy or Psoralen and Ultraviolet A (PUVA) treatment should be monitored for Non-Melanoma Skin Cancer (NMSC).* • *PL Section- 2* Legal status: *Prescription only medicine* *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.* Additional risk minimisation measures: None
Important Potential risk: Cardiovascular Events	
Evidence for linking the risk to medicine	The risk of developing cardiovascular (CV) events in subjects on anti-IL-12/23p40 therapy such as with the reference product 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, of the reference product Stelara in psoriasis, resulting predominantly from an imbalance in event rates from a smaller Phase 2 trial. Additional analyses performed internally by the MAH of reference product Stelara show that the overall rates of myocardial infarction and stroke with up to 5 years of treatment with the reference product 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 minimisation measures	Routine risk minimisation measures: None Legal status: *Prescription only medicine* *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.* Additional risk minimisation measures: None
Important Potential risk: Serious depression including suicidality	
Evidence for linking the risk to medicine	Psoriasis patients can have an increased risk for depression and, in rare cases, suicide. Depression has been identified as an ADR for Stelara and Steqeyma (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 of the reference product Stelara. The incidence of serious depression including suicidality across indications remains low. The available safety data from clinical studies and post marketing experience with the reference product Stelara 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 and Steqeyma.
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 minimisation measures	Routine risk minimisation measures: • *SmPC Section 4.8* • *PL Section- 4* Legal status: *Prescription only medicine* *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.* Additional risk minimisation measures: None
Important Potential risk: Venous thromboembolism	
Evidence for linking the risk to 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 immobilisation, hospitalisation, surgical interventions, oral contraceptive use, etc.). 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 the reference product 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 post marketing data with the reference product Stelara, 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 minimisation measures	Routine risk minimisation measures: None Legal status: *Prescription only medicine* *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.* Additional risk minimisation measures: None
Important potential risk: Exposure during pregnancy	
Evidence for linking the risk to 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/foetal 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 non-clinical 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 foetus and are recommended to be avoided during pregnancy.

	A recent update on the safety of IBD medications in pregnancy summarised 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 minimisation measures	Routine risk minimisation measures: • *Guidance is given in the SmPC Section 4.6 to avoid the use of Steqeyma in pregnancy and use of effective methods of contraception are recommended during and 15 weeks after treatment.* • *PL Section- 2* Legal status: *Prescription only medicine* *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.* Additional risk minimisation measures: None
Missing information: Long-term safety in paediatric psoriasis patients 6 years and older	
Risk minimisation measures	Routine risk minimisation measures: None Legal status: *Prescription only medicine* *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.* Additional risk minimisation measures: None
Missing information: Long-term impact on growth and development in paediatric psoriasis patients 6 years and older	
Risk minimisation measures	Routine risk minimisation measures: None Legal status: *Prescription only medicine* *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.* Additional risk minimisation measures: None
Missing information: Long-term safety in adult patients with moderately to severely active Crohn's disease	
Risk minimisation measures	Routine risk minimisation measures: None Legal status: *Prescription only medicine* *Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.* Additional risk minimisation measures: None

Abbreviations: ADR; Adverse Drug Reaction, AEs; Adverse Events, CD: Crohn's Disease, CI; Confidence Interval, CV; Cardio Vascular, IBD; Inflammatory Bowel Disease, MAC; Mycobacterium intracellular complex, MACE: Major Adverse Cardiovascular Event, MTX; Methotrexate, NMSC: Non-Melanoma Skin Cancer, NTM; Non-TB

mycobacterial (NTM), OR; Odds Ratio, PL: Package Leaflet; PsA; Psoriatic arthritis, PUVA: Psoralen and Ultraviolet A, PY; Patient year, SmPC: Summary of Product Characteristics, TB: Tuberculosis, TNF: Tumour necrosis factor, US; United States, UV; Ultra Violet, VTE; Venous Thromboembolism.

II.C Post-authorisation development plan

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

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

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

There are no other studies in post-authorisation development plan of Steqeyma.

Part VII: Annexes

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Annex 4 – Specific adverse drug reaction follow-up forms

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

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

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

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

1. Medical History and Concurrent Conditions

☐Prior history of exposure to TB
Details:
☐Prior history of exposure to Hepatitis B/C
Details:
Details of vaccination history:
☐The patient was considered immunocompromised (underlying diagnoses, immunosuppressive therapy ets.)
Details:
Other relevant medical history or any known risk factors for acquiring specific infection in question:

2. Adverse Event Details

☐The infection was present prior to starting the product
☐There were unusual features of the patient's presentation or clinical course
Details:
Type of infection (e.g., pneumonia, endocarditis, ets.) and location if relevant (e.g., subcutaneous abscess of the forearm or TB of the CNS):

Thank you for completing this form.

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

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

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

☐Weight loss ≥10% of ideal body weight ☐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, refugee camp, etc.)
Details:

2. Diagnostics

☐Purified Protein Derivative (PPD) testing was performed. Indicate test used:
☐Intradermal skin test
☐Multipuncture skin test
Number of units administered:
PPD Result: mm of induration (0, if no induration)
Date of PPD: [dd-MMM-yyyy]
2nd PPD results (if applicable): mm of induration
Date of second PPD: [dd-MMM-yyyy]
☐False negative test (e.g., time of injection to time of evaluation too long/short, evaluator of induration, etc.)? Explain reasons:

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

Other laboratory results

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

Thank you for completing this form.

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

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

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

☐Previous malignancy (Provide specific diagnosis):

☐Occupational/Exposure history:

☐Excessive sub exposure (Describe):

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

☐History of radiation

Dose of radiation:

Area treated:

Age (or date of therapy) of the patient when they were treated with radiation:

Indication for radiation:

Any radiation induced changes?

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

Viral infection: ☐EBV ☐HIV ☐HPV ☐HBV or HCV

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

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

☐In first degree relatives:

☐In more distant relatives:

☐Previous history of tumor necrosis factor (TNF) blocker therapy (With medication names, dates of exposure and the total number of doses or an approximation):

Age at first exposure to any TNF blocker:

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

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

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

☐Cytogenetic abnormalities detected at any point in time? (Include those relevant for any

malignancy including myeloma – this could be germline genetic diseases predisposing for malignancy e.g., Down's syndrome, neurofibromatosis etc., or cytogenetic abnormalities relevant to myeloma)

2. Diagnostics

Histopathologic diagnosis (Include the histopathology report):

Include malignancy stage, location of primary tumor, metastases, lymph node involvement and staging system used:

Additional diagnostic information, including finding that support specified staging; specialty consultations (Attach reports, if available): Final diagnosis:

☐**Lymphoma**

☐Non-Hodgkin's lymphoma

Histologic subtype: Immunophenotype: Cytogenetics:

☐Hodgkin's lymphoma

Histologic subtype:

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

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

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

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

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

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

3. Treatment

What was the response to the first treatment for malignancy?

☐Complete response ☐Partial response ☐Stable disease ☐Progressive disease

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Thank you for completing this form.

Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Cardiovascular Event

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

1. **Drug details:**

   Number of doses (e.g., injections, infusions) given prior to cardiovascular event:

   Recent dose change? Details:
   When did the patient last receive the product before the current dose?
   Date: [dd-MMM-yyyy], Time:

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

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

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

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

   Relevant family history:

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

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

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

Thank you for completing this form.

Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Venous Thromboembolism (VTE)

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

1. Adverse Event Description

Patient's clinical signs and symptoms

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

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

2. Medical history and Concurrent Conditions

Provide details:

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

Genetic risk factors:

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

Acquired risk factors:

☐Reduced mobility (paralysis, paresis, travel etc.) ☐Recent surgery
☐Indwelling central venous catheters ☐Recent trauma
☐Recent discontinuation of anticoagulants (e.g., heparin, warfarin, DOACs)
☐Hormone replacement therapy (HRT) ☐Hormonal contraceptives
☐Polycystic ovary syndrome (PCOS) ☐Pregnancy
☐Postpartum (up to 3 months after childbirth)
☐Phlebitis ☐Lupus
☐Inflammatory bowel disease ☐Myeloproliferative disorders
☐Diabetes mellitus ☐Hyperlipidemia
☐Hypertension ☐Dehydration
☐Other significant medical co-morbidities or risk factors for DVT, specify:
If yes to any of the above, provide details:

Provide Well's score, if calculated:

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

Diagnostic Test	Results at baseline or prior to use of product (Include date and value/details)	Test results after use of product (Include date and value/details)
CBC with smear (microscopic evaluation)		
ESR		
Platelet count		
Antibodies to platelet factor 4 (PF4)		
Fibrinogen levels		
Clauss fibrinogen assay		
D-Dimer		
Clotting Profile (PT, aPTT-prior to an anticoagulation treatment)		
Thrombin time (Bovine) Plasma		
Prothrombin		
Antithrombin activity		
Factor V Leiden		
Protein C activity		
Protein S activity		
C-reactive protein		
Homocystein levels		
Dilute Russells Viper Venom Time (DRVVT), Plasma		
Activated Protein C Resistance V (APCRV), Plasma		
Thrombophilia interpretation		
Anticardiolipin antibodies (IgG and IgM) or beta-2 glycoproteins antibodies		
Antiphospholipid antibodies (IgG and IgM)		
Lupus anticoagulant		
Heparin antibodies		

ANA and ANCA		
IL6 levels		
ADAMTS13 Activity Assay		
Ceruloplasmin		
Direct Coombs test		
Complement C3, C4		
Methylenetetrahydrofolate reductase gene mutation		
Prothrombin gene mutation (G20210A)		
Occult blood in stool		
COVID-19 test		
Troponins		
Brain Natriuretic Peptide		
Arterial Blood Gases		
Chest X-Ray		
Electrocardiography		
Echocardiography		
Duplex Ultrasonography		
MRI scan		
CT scan		
Contrast Venography		
Pulmonary Angiography		
Ventilation-Perfusion Scanning		

Provide details of any additional diagnostic results:

Thank you for completing this form.

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

Not applicable as there are no proposed additional risk minimisation activities.