RISK MANAGEMENT PLAN

for

Usrenty® (ustekinumab)

Data lock point (DLP) for RMP: 30-Sep-2024

Version Number: 0.1

Dated: 02-May-2025

[redacted]

Risk Management Plan – Ustekinumab

Risk Management Plan for:	Ustekinumab
RMP Version number:	0.1
Data lock point for this RMP:	30-Sep-2024
Date of final sign off:	02-May-2025
Rationale for submitting an updated RMP:	Not applicable; this is the initial RMP
Summary of significant changes in this RMP:	Not applicable; this is the initial RMP
Other RMP versions under evaluation • RMP version number • Submitted on • Procedure number	Not applicable
Details of the currently approved RMP • Version number • Approved with procedure • Date of approval (Opinion date)	Not applicable; this is the initial RMP
QPPV name	Sanja Prpic
Signature	[redacted]
E-mail address of contact person	[redacted]

Table of Contents

List of Tables

List of Abbreviations

Abbreviation	Definition
ADA	Anti-Drug Antibody
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the concentration-time curve
AUC_{0-t}	Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (t_{last})
AUC_{0-inf}	Area under the concentration-time curve from time 0 extrapolated to infinity
AUC_{0-inf}/P	Investigational medicinal product protein-content adjusted area under the concentration -time curve from time 0 extrapolated to infinity
BCG	Bacillus Calmette-Guérin
CD	Crohn's disease
CI	Confidence interval
CV	Cardiovascular
DLP	Data Lock Point
DMARD	Disease-modifying anti-rheumatic drug
DNA	Deoxyribonucleic Acid
DSUR	Development safety update report
EMA	European Medicines Agency
EOS	End-of-study
EPAR	European public assessment report
EU	European Union
FDA	Food and Drugs Administration
GLSMs	Geometric least square means
GVP	Good Pharmacovigilance Practices
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLT	High Level Term
IBD	Inflammatory bowel disease
ICF	Informed consent form
ICH	International Council for Harmonisation

ICSR	Individual Case Safety Report
IL	Interleukin
IV	Intravenous
LSR	Local Safety Responsible
MAC	Mycobacterium intra cellulare complex
MI	Myocardial Infarction
MTX	Methotrexate
NMSC	Non-melanoma skin cancer
NOAEL	No Observed Adverse Effect Level
NTM	Nontuberculous mycobacteria
PBRER	Periodic Benefit Risk Evaluation Report
PK	Pharmacokinetic
PsA	Psoriatic arthritis
PSUR	Periodic Safety Update Report
PT	Preferred Term
PUVA	Psoralen and ultraviolet A
PVD	Pharmacovigilance department
TB	Tuberculosis
TK	Toxicokinetic
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
RPP	Responsible Person for Pharmacovigilance
SC	*Subcutaneous*
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOP	Standard Operating Procedure
TB	Tuberculosis
USFDA	United States Food and Drug Administration
VTE	Venous Thromboembolism

Part I: Product(s) Overview

Table 1: Product overview

Active substance (s) (INN or common name):	Ustekinumab
Pharmacotherapeutic group (s): (Anatomical Therapeutic Chemical Classification System (ATC) Code):	Immunosuppressants, interleukin inhibitors, ATC Code: L04AC05
Marketing Authorisation Applicant:	Biocon Biologics Limited
Medicinal products to which this RMP refers	Ustekinumab (Usrenty (Bmab1200))
Invented name (s)in the European Economic Area (EEA)	Usrenty
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Monoclonal antibody
	Summary of mode of action: Ustekinumab is a fully human IgG 1κ monoclonal antibody (mAb) product with a molecular weight of approximately 148,600 Daltons. Ustekinumab binds human and primate interleukin (IL)-12/23p40 protein with specificity. Ustekinumab prevents the binding of IL-12 or IL-23 to the cell surface IL-12Rβ1 receptor, and thereby blocks receptor signaling. In this manner, ustekinumab inhibits the composition biological activity of IL-12 and IL-23 in all in vitro assays examined.
	Composition: Usrenty 130 mg concentrate for solution for infusion. Usrenty 45 mg solution for injection. Each vial contains 45 mg ustekinumab in 0.5 mL. Usrenty 45 mg solution for injection in pre-filled syringe Each pre-filled syringe contains 45 mg ustekinumab in 0.5 mL. Usrenty 90 mg solution for injection in pre-filled syringe

	Each pre-filled syringe contains 90 mg ustekinumab in 1 mL. Important information about its composition: Ustekinumab is a fully human IgG1κ monoclonal antibody to interleukin (IL)-12/23 produced in a murine myeloma cell line using recombinant DNA technology. List of excipients: L-histidine L-histidine monohydrochloride monohydrate L-methionine Polysorbate 80 Sucrose Sodium hydroxide (for pH adjustment) Hydrochloric acid (for pH adjustment) Water for injections
Hyperlink to the Product Information	Usrenty Product information (Module 1.3.1)
Indication (s) in the EEA	Current: **Plaque psoriasis** Usrentyis 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** Usrenty 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). **Psoriatic arthritis** Usrenty, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. **Crohn's Disease** Usrenty is indicated for the treatment of adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.
	Proposed: Not applicable.

Dosage in the EEA	Current: **Posology** **Plaque psoriasis** The recommended posology of Usrenty is an initial dose of 45 mg administered subcutaneously, followed by 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 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. **Psoriatic arthritis (PsA)** The recommended posology of Usrenty is an initial dose of 45 mg administered subcutaneously, followed by 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment. **Paediatric plaque psoriasis (6 years and older)** The recommended dose of Usrenty based on body weight is presented in the Summary of Product Characteristics (SmPC) under section 4.2 (Posology and method of administration) Usrenty should be administered at Weeks 0 and 4, then every 12 weeks thereafter. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment. **Crohn's Disease** In the treatment regimen, the first dose of Usrenty is administered intravenously. For the posology of the intravenous dosing regimen, see section 4.2 of the Usrenty 130 mg Concentrate for solution for infusion SmPC. The first subcutaneous administration of 90 mg Usrenty should take place at week 8 after the intravenous 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. Immunomodulators and/or corticosteroids may be continued during treatment with Usrenty. In patients who have responded to treatment with Usrenty, corticosteroids may be reduced or discontinued in accordance with standard of care. In Crohn's disease, if therapy is interrupted, resumption of treatment with subcutaneous dosing every 8 weeks is safe and effective.
	<u>Proposed</u>: Not applicable.
Pharmaceutical form (s) and strengths	<u>Current</u>: *For Subcutaneous (SC) use* The solution is clear, colourless to light yellow. Solution for injection in vial: 45 mg/0.5 mL. Solution for injection in pre-filled syringe: 45 mg/0.5 mL and 90 mg/1 mL. *For Intravenous (IV) use* The solution is clear, colourless to light yellow. Concentrate for solution for infusion:130 mg/26 mL (5 mg/mL).
	<u>Proposed</u>: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety Specification

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

Not applicable as this RMP pertains to a similar biologic. (Ref: In accordance with the Good Pharmacovigilance Practices (GVP) - Biological medicinal products. "All parts of an RMP are required for a biosimilar, except for RMP part II, module SI "Epidemiology of the target population).

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

No pharmacokinetic (PK), toxicokinetic (TK), Anti-Drug Antibody (ADA) evaluation and toxicology have been performed yet for Usrenty (Bmab1200)

Based on appropriate FDA and EMEA guidelines as well as the feedback received from the FDA type 2 meeting (Reference ID: 4796456) and EMA Scientific Advice (EMEA/H/SA/4410/1/2020/III) in vivo studies are deemed not necessary for the establishment of biosimilarity, as functional assays performed as a part of primary pharmacodynamics are highly sensitive in detecting differences between Usrenty (Bmab1200), US-Licensed Stelara® and EU-Approved Stelara®.

The results of pivotal non-clinical toxicity study in cynomolgus monkeys reported for the Stelara® is summarized below.

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

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

Key Safety Findings	Relevance to Human Usage
<u>Toxicity</u> **Repeat-dose toxicity**	
Nonclinical safety studies showed that ustekinumab was well tolerated in general developmental, and reproductive toxicity studies following weekly IV or twice weekly SC dosing at doses up to 45 mg/kg.	Based on animal studies, there is a large safety margin for humans administered ustekinumab IV and SC (up to 7.5- and 45-fold higher than the human dose, respectively).
Reproductive toxicity	
Repeated dose toxicology studies conducted in cynomolgus monkeys showed no toxicological effects of ustekinumab on reproductive organs. The no-observed-adverse-effect level (NOAEL) of ustekinumab for general toxicity and reproductive function of male cynomolgus monkeys was 45 mg/kg, approximately 45-fold higher than the	Results of reproductive toxicity studies suggest that administration of ustekinumab is unlikely to adversely affect male or female fertility.

Key Safety Findings	Relevance to Human Usage
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.	
Developmental toxicity	
The NOAEL of ustekinumab for maternal toxicity and for development of the conceptus was 45 mg/kg following weekly IV dosing or twice weekly SC dosing of pregnant monkeys, approximately 45-fold higher than the anticipated human dose.	Results of developmental toxicity studies suggest that administration of ustekinumab will not adversely affect mothers or their offspring.
Genotoxicity	
Genotoxicity studies have not been conducted with ustekinumab. The standard battery of assays recommended for small molecules is primarily designed to detect substances that interact with deoxyribonucleic acid (DNA) and induce gene mutations, chromosome aberrations and/or DNA damage and is not applicable to biotechnology-derived pharmaceuticals (ICH S6).	Monoclonal antibodies such as ustekinumab are not expected to pass through the cellular and nuclear membranes of intact cells and interact with DNA or other chromosomal material; therefore, potential genotoxicity is unlikely.
Carcinogenicity	
The risk of malignancy is a safety concern for immune modulating drugs in general. Carcinogenicity studies were not conducted with ustekinumab. Direct evaluation of carcinogenic potential of ustekinumab in carcinogenicity studies are precluded by its limited species reactivity. Ustekinumab only binds human and non-human primate IL-12p40 but does not bind to or neutralize IL-12 or IL-23 from mice or rats. There are no validated non-rodent models of carcinogenicity. Studies suggesting malignancy risk from antagonism of IL-12 include experiments using primarily mouse nonclinical tumor models. These studies have typically shown anti-tumor activity of exogenously administered IL-12 (Brunda 1993)[7] or demonstrated compromised host defense to neoplasia following either antagonism of rodent IL-12 activity by anti-murine IL-12 antibodies or genetic ablation ofIL-12 activity in knockout mice (Airoldi 2005)[10]. While data from these studies suggest a possible carcinogenic hazard associated with IL-12 antagonism, they are	There is a theoretical risk of malignancy associated with administration of ustekinumab based on the scientific literature pertaining to antagonism of IL-12/23p40. Malignancy is an important potential risk for ustekinumab.

Key Safety Findings	Relevance to Human Usage
not adequate or validated to support a carcinogenic risk assessment.	
<u>Other</u> **Hepatotoxicity and nephrotoxicity** No evidence of hepatotoxicity or nephrotoxicity was observed in toxicity studies based on clinical pathology and histopathology evaluations. **Infection** The risk of infection is a safety concern for immune modulating drugs in general. Infection studies were not conducted with ustekinumab because there are no validated non-rodent models of infection in which ustekinumab would have pharmacological activity. Published rodent studies suggesting infection risk from inhibition of Th1 or Th17 indicated that IL-12 and IL-23 may contribute to protective immune responses to viral, bacterial, intracellular protozoa, and fungal pathogens (Chackerian 2006)[8]; (Torti 2007). One of the 16 monkeys in the high-dose (45 mg/kg group) developed bacterial enteritis in Week 26 of the 6-month SC toxicology study. The possibility of ustekinumab-related contribution to this infection could not be excluded.	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). There is a theoretical risk of infection associated with administration of ustekinumab based on the scientific literature pertaining to inhibition ofIL-12/23p40. Serious infections (including mycobacterial and salmonella infections) is an important potential risk for Ustekinumab.

Summary of Nonclinical Safety Concerns

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

Part II: Module SIII - Clinical trial exposure

This biosimilar product has been developed in accordance with relevant European (EMEA/H/SA/4410/1/2020/III) and United States Food and Drug Administration (USFDA) (FDA type 2 meeting (April 26, 2021): Reference ID- 4796456 FDA type2 meeting (October 6, 2021): Reference ID- 4882528) guidelines.

Clinical trial development programme for Usrenty (also denoted Bmab1200 during development) consisted of the following two clinical trials (BM12H-NHV-01-G-01 and BM12H-PSO-03-G-02) that aimed to establish biosimilarity of Bmab1200 with the reference medicinal product, Stelara® in terms of pharmacokinetics, pharmacodynamics, safety and efficacy.

- Study **BM12H-NHV-01-G-01**: A Phase 1, Randomized, Double-blind, 3-arm, Parallel Design Study in Healthy Subjects to Evaluate Pharmacokinetics, Safety, Tolerability, and Immunogenicity of Bmab1200. After Single Subcutaneous Injection in Comparison with EU-approved Stelara® and US-licensed Stelara®.

- Study **BM12H-PSO-03-G-02**: A Randomized, Double-Blind, Parallel Group, Multicenter, Phase 3 Study to Compare the Efficacy and Safety of Bmab1200 and Stelara® in Patients with Moderate to Severe Chronic Plaque Psoriasis.

Overall, 384 patients in Phase 3 and 258 subjects (healthy volunteers) in Phase 1 trial have been enrolled into 2 clinical trials and 284 patients and 86 subjects have received Bmab1200 since DIBD (02 Mar 2022). Study BM12H-NHV-01-G-01 completed on 13 October 2023 and Study BM12H-PSO-03-G-02 completed on 13-Mar-2024.

Study BM12H-NHV-01-G-01: (Status: Completed)

Study Design

This was a Phase 1, multi-center, randomized, double-blind, 3-arm, parallel group study to establish PK similarity between Bmab1200, US Stelara, and EU Stelara after a single 45 mg subcutaneous injection in healthy male and female subjects. Up to 258 subjects were to be enrolled to ensure that at least 246 subjects completed the study.

Potential subjects were screened to assess their eligibility to enter the study within 28 days prior to the dose administration. Subjects were admitted into the study site on Day -1 and were confined to the study site until discharge on Day 10. Subjects returned to the study site for follow-up visits up to Day 113 (±2 days).

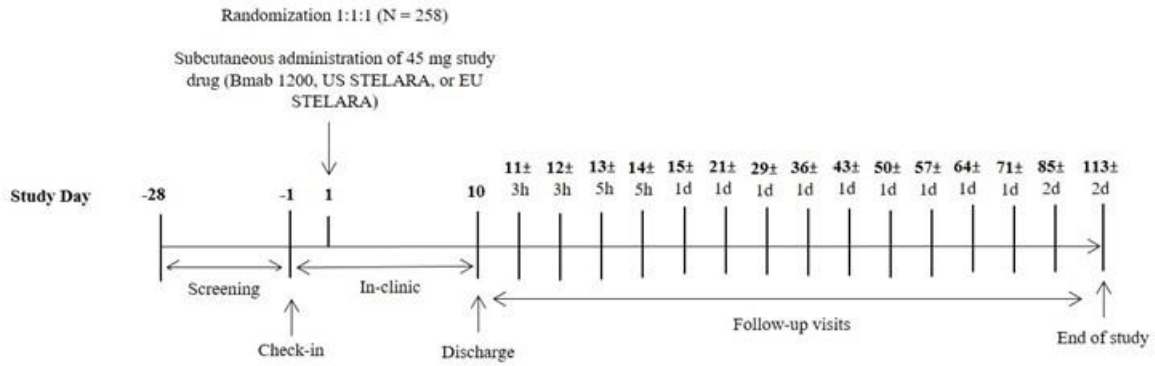
Subjects were randomized in a 1:1:1 ratio to receive a single dose of 45 mg study drug on Day 1 as either:

- US Stelara
- EU Stelara, or
- Bmab1200.

The total duration of study participation for each subject (from screening through end-of-study [EOS] visit) was anticipated to be approximately 20 weeks.

The start of the study was defined as the date the first subject signed an Informed consent form (ICF). The point of enrolment occurred at the time of subject number allocation. The end of the study was defined as the date of the last subject's last assessment (scheduled or unscheduled).

A schematic of the study design is presented below



Overall, 258 subjects were randomized and dosed in the study. Of them, 257 subjects (99.6%) completed the study in accordance with the protocol and protocol amendment. One subject who had received 45 mg US Stelara withdrew consent and was discontinued from the study.

Subject disposition for the safety population is summarized in the table below.

	45 mg Bmab1200 (N = 86)	45 mg US Stelara (N = 87)	45 mg EU Stelara (N = 85)	Overall (N = 258)
Randomized	86	87	85	258
Dosed	86	87	85	258
Completed the Study	86 (100%)	86 (98.9%)	85 (100%)	257 (99.6%)
Discontinued the Study	---	1 (1.1%)	---	1 (0.4%)
Withdrawal by Subject	---	1 (1.1%)	---	1 (0.4%)
Population				
Safety	86 (100%)	87 (100%)	85 (100%)	258 (100%)
Pharmacokinetic	86 (100%)	85 (97.7%)	84 (98.8%)	255 (98.8%)

n = number of subjects with valid observations; N = number of subjects; % = percentage of subjects with valid observations (n/N×100)
For ' Dosed ' category, n statistics presented; for all other categories, n (%) statistics presented.
Reference: Table 14.1.1.2.1
ProgramLocation:/cvn/projects/prj/ecb/programs/000000226840/dev/tables/t_ds_itt.sas
Program Status: FINAL Program Run: 27sep2023 Protocol Reference: BM12H-NHV-01-G-01

Two hundred and fifty-eight (100.0%) subjects received the study drug per planned dose. Overall, 86 subjects received a single dose of 45 mg Bmab1200, 87 subjects received a single dose of 45 mg US Stelara, and 85 subjects received a single dose of 45 mg EU Stelara on Day 1 as per the randomization schedule.

Pharmacokinetics Conclusions

- Following a single subcutaneous dose of 45 mg Bmab1200, US Stelara, and EU Stelara, the median time to maximum ustekinumab serum concentrations (t_{max}) and mean maximum ustekinumab serum concentrations (C_{max}) were similar. Concentration-time profiles were characterized by a monophasic decline with a slow terminal elimination phase.
- Statistical analysis demonstrated PK similarity as the 90% Confidence interval (CI)s of Geometric least square means (GLSMs) ratio for both primary PK parameters ($AUC_{0\text{-}inf}$ and C_{max}), as well as $AUC_{0\text{-}t}$, were entirely contained within the predefined bioequivalence range of 0.8000 and 1.2500 for each of the 3 pairwise comparisons Bmab1200 [Test] versus the US Stelara [Reference]; Bmab1200 [Test] versus the EU Stelara [Reference]; and the US Stelara [Test] versus the EU Stelara [Reference]).
- Statistical analysis of protein-adjusted primary PK parameters ($AUC_{0\text{-}inf}$/P and C_{max}/P) supported PK similarity between Bmab1200, the US Stelara, and the EU Stelara as the 90% CIs of GLSMs ratio (Test/Reference) fell within the bioequivalence range of 0.8000 and 1.2500.
- The point estimates of GLSMs ratio (Test/Reference) of both primary PK parameters ($AUC_{0\text{-}inf}$ and C_{max}) fell within the predefined limits of 0.8000 to 1.2500 for both the Japanese and non-Japanese populations, supporting PK similarity between Bmab1200, the US Stelara, and the EU Stelara irrespective of ethnic origin.

Immunogenicity

- The incidence of ADA positivity ranged from 64.0% to 86.2%. The analysis supported that the overall absorption and exposure were unaffected by the presence of ADA with the titers observed as GLSM and 90% CI were within the range of 0.800 to 1.2500. Also, mean $t_{1/2}$ values were comparable among the 3 treatment groups, ranging from 20.5 to 22.1 days.
- The number of subjects who were ADA- at baseline and ADA+ post-dose at any given timepoint until the EOS visit was lower in the Bmab1200 group compared to the EU Stelara and the US Stelara treatment groups.

Safety summary

- Overall, 180 subjects reported a total of 435 TEAEs during the study, the majority of which were mild (61.6% of subjects [323 TEAEs]) or moderate (27.9% of subjects [107 TEAEs]) in severity. The majority of TEAEs were considered not related to study drug and there were no apparent differences in treatment related TEAEs between treatment groups.
- There were 2 SAEs reported by 2 subjects and these events did not result in discontinuation from the study and were not considered to be related to the study drug. Neither of the SAEs were considered to impact the known safety profile of the investigational drug. No deaths occurred during the study.
- There were no TEAEs leading to discontinuation and no other clinically meaningful events during the study. There were no clinical laboratory findings or vital signs findings considered to be of clinical importance or which indicated safety concerns for any treatment group.

Overall, there were no safety concerns related to incidence or titers of ADA in any of the treatment groups.

Conclusions

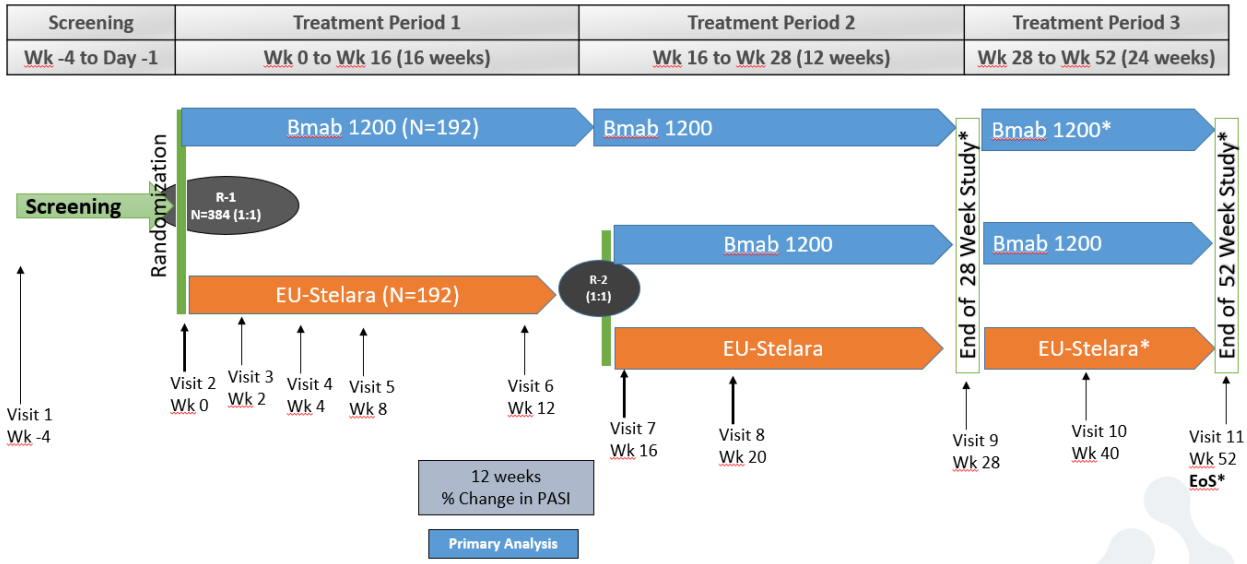
- Following a single subcutaneous dose of 45 mg Bmab1200, US Stelara, and EU Stelara, the median time to maximum ustekinumab serum concentrations and mean maximum ustekinumab serum concentrations were similar. Concentration-time profiles were comparable and characterized by a monophasic decline with a slow terminal elimination phase.
- Statistical analysis demonstrated PK similarity for PK parameters ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max}) between Bmab1200, the US Stelara, and the EU Stelara as the 90% CIs of GLSMs ratio (Test/Reference) fell within the predefined bioequivalence range of 0.8000 and 1.2500 (i.e., 80.00% and 125.00%).
- A single dose of 45 mg Bmab1200 was generally safe and well tolerated in healthy subjects across the 3 treatment groups. The majority of the events were mild in severity and were considered not related to the study drugs.

Study BM12H-PSO-03-G-02 (Status: Completed)

Study Design

This was a randomized, double-blind, active-controlled, parallel group, multicenter study designed to compare efficacy, safety, immunogenicity, and PK of Bmab1200 with Stelara in adult patients with moderate to severe chronic plaque psoriasis. The study was planned to be conducted in Europe and North America across approximately 42 sites in 6 countries. The study was conducted in an outpatient setting, and the participation for each patient consisted of a screening period (up to 4 weeks/28 days) and a double-blind, active controlled treatment period (52 weeks) with a rerandomization step for switching therapy at Week 16 (before dosing). The total duration of the study (excluding the screening period) will be 52 weeks.

A schematic of the study design is presented below



Abbreviations: EOS, end of study; EU, European Union; FDA, Food and Drug Administration; PASI, Psoriasis Area and Severity Index; R-1, randomization; R-2, rerandomization; US, United States; Wk, Week.

*The US FDA had agreed to a 28-week study, while the extended study to fulfill the Pharmaceuticals and Medical Devices Agency requirement will continue and end at Week 52.

Note: Study treatment was to be administered at a dose of 45 mg or 90 mg (based on body weight category) at the baseline visit, Week 4, Week 16, Week 28, and Week 40.

To maintain the study blinding, the patients in the original Bmab1200 group also went through the rerandomization procedure; however, they were assigned and continued to receive Bmab1200.

In Study BM12H-PSO-03-G-02, 384 patients with plaque psoriasis were initially randomized in a 1:1 ratio to receive Bmab1200 or EU-approved Stelara®. Out of 384 patients, 191 were enrolled to receive Bmab1200 and 193 patients were enrolled to receive Stelara®in TP1. Most of these patients (378 patients; 98.4%) were included in the Per-Protocol Set (PPS) (189 patients [99.0%] in the Bmab1200 group and 189 patients [97.9%] in the Stelara® group) and received at least 2 study treatment administration (baseline and Week 4). Overall, 382 patients (99.5%) completed treatment in TP1; 11 patients (2.9%) completed TP1 did not enter TP2. Overall, 40 patients (10.4%) withdrew from the study. Of these, many patients were followed until the Week 28 visit per the protocol. A total of 371 patients completed the Week 28 visit. Thus, a total of 371 patients were rerandomized and entered TP2. All 371 patients completed treatment in TP2 (defined as having received treatment at Week 16). Twenty-three patients were discontinued from TP2 because of unblinding issues related to rerandomization at Week 16 and an additional 4 patients were discontinued from TP2 (2 patients at the Investigator's discretion because of medical or administrative reasons, 1 patient withdrew consent, and 1 patient was lost to follow-up). Thus, 344 patients completed TP2 (defined as having answered "yes" to the Week 28 TP2 completion question in the eCRF). Of these, 11 patients (2.9%) who completed TP2 did not enter TP3 (defined as not having answered "yes" to the Week 28 TP3 participation question in the eCRF and not having been dosed at Week 28). Thus, a total of 333 patients entered and were dosed in TP3. A total of 324 patients (84.4%) completed the study. (ie, overall, 60 patients [15.6%] were withdrawn from the study).

Safety Summary

- Treatment compliance was 100% for all patients in TP1, TP2, and TP3.
- Both products were safe and well tolerated through the study (across all 3 treatment periods TP1, TP2, and TP3). The overall incidence of individual TEAEs was low; 210 patients (54.7%) reported 492 TEAEs through the study (baseline through Week 52). The most frequently reported TEAEs were from the SOCs of infections and infestations (111 patients; 28.9%), investigations (67 patients; 17.4%), and metabolism and nutrition disorders (25 patients; 6.5%). The remaining SOCs occurred in ≤5% of patients. Nasopharyngitis was

the most frequently reported TEAE (32 patients; 8.3%), followed by alanine aminotransferase increased (20 patients; 5.2%) and blood triglycerides increased (17 patients; 4.4%). The majority of TEAEs were Grade 1 and Grade 2 in severity.

- The size of the group of patients who received Stelara throughout the study was approximately half the size of the group of patients receiving Bmab1200 due to the switch after rerandomization. When analysing the data through the study (baseline through Week 52) for patients who remained on Bmab1200 or Stelara:
    - The percentages of patients who experienced TEAEs were comparable in the Bmab1200 group and Stelara-Stelara groups. There were 58.1% of patients in the Bmab1200 group and 47.5% of patients in the Stelara group who experienced TEAEs, while 13.1% of patients and 10.9% of patients, respectively, experienced treatment related TEAEs. The majority of TEAEs were Grade 1 or Grade 2 in severity.
    - There were 6.8% of patients in the Bmab1200 group and 5.0% of patients in the Stelara group who had Grade ≥3 TEAEs. Of the Grade ≥3 treatment related AEs in the study, 2 patients (1.0%) had 6 TEAEs in the Bmab1200 group.
    - The most common TEAEs of special interest in both groups were in the category of infections (30.4% of patients in the Bmab1200 group and 20.8% of patients in the Stelara group). Nasopharyngitis was the most frequently reported TEAE in both groups (9.4% in the Bmab1200 group vs 5.9% in the Stelara group). Both TEAEs of special interest of malignancy (PT: endometrial adenocarcinoma and squamous cell carcinoma of the tongue) occurred in 2 patients (1.0%) in the Bmab1200 group. One patient (0.5%) in the Bmab1200 group and 3 patients (3.0%) in the Stelara group experienced TEAEs of special interest of hypersensitivity reactions. All were considered to be treatment-related, and the majority of TEAEs of special interest were Grade 1 or Grade 2 in severity and were assessed as non-serious. Only the 2 TEAEs of special interest of malignancy were assessed as serious. The incidence of individual TEAEs of special interest of infections are generally consistent with those reported in previous comparative studies of similar nature and duration with Ustekinumab.
- No patients experienced TEAEs leading to death through the study.
- The incidence of serious TEAEs was low. Overall, 7 patients (1.8%) experienced 9 serious TEAEs through the study; 1 patient in the Bmab1200 group had 2 serious TEAEs (abdominal pain and cholestatic jaundice) that were related to study treatment.
- Overall, the number of patients who experienced TEAEs leading to study treatment withdrawal and study discontinuation was low in the study. Six patients (1.6%) experienced 7 TEAEs leading to study treatment withdrawal that also led to study discontinuation: 3 patients (1.6%) with 4 TEAEs in the Bmab1200 group and 3 patients (3.0%) with 3 TEAEs in the Stelara-Stelara group. No patients in the Stelara-Bmab1200 group had TEAEs leading to study treatment withdrawal.
- Overall, there were no clinically relevant changes in vital signs, ECGs, clinical laboratory data, or physical examinations during the study.
- Overall, Bmab1200 showed a favorable safety profile through the study that was similar to the Stelara safety profile.

Conclusions

- Results demonstrate equivalent efficacy between Bmab1200 and Stelara in patients with moderate to severe chronic plaque psoriasis for the primary efficacy endpoint (percentage change from baseline in the PASI score at Week 12).
- The efficacy of Bmab1200 was comparable with that of Stelara for the secondary efficacy endpoints at earlier and later time points throughout the study.
- Efficacy continued to improve in the 3 treatment groups comparably at Week 20 and Week 28, and improvements were maintained at Week 40 and Week 52.

- The safety results demonstrate Bmab1200 is well tolerated in comparison to Stelara in patients with moderate to severe chronic plaque psoriasis, and this continued to be demonstrated through the study. From Week 28 through Week 52, the safety profile remained favorable, with TEAEs of special interest being only in the infections category, of mild and moderate severity, and non-serious. After Week 28, there were no more TEAEs of special interest of hypersensitivity or malignancy reported.
- The majority of the TEAEs were mild or moderate in severity and were deemed unrelated to the study treatment. The nominal differences of certain TEAEs are incidental and are not clinically meaningful.
- The safety of ustekinumab did not appear to be compromised by the switch at Week 16 (Stelara to Bmab1200).
- Longer exposure until Week 52 did not result in any safety concerns with Bmab1200 administration and is comparable with Stelara.
- The serum concentration and immunogenicity profile noted in the study did not result in any treatment-related differences in efficacy and safety. While the ADA rates observed in both treatment groups were high, the level of ADA-positivity is attributed to the highly sensitive drug-tolerant ADA method used in the study, with a high sensitivity.

The estimated exposure of Bmab1200, BM12H-PSO-03-G-02 (Phase 3) is provided in the below tables.

SIII.1 Duration of Exposure

Total exposed population (N=191)		
Duration of exposure	**Persons (%)**	**Person time (person-years)***
≥ 0 Week to <2 Week	1(0.52)	0.003
≥ 2 Week to <**4** Week	0	0
≥ 4 Week to <**8** Week	5(2.62)	0.394
≥ 8 Week to <**12**Week	0	0
≥ 12 Week to <**16**Week	3(1.57)	0.901
≥ 16 Week to <20Week	14(7.33)	4.359
≥ 20 Week to <**28**Week	28(14.66)	14.773
≥ 28 Week to <**40**Week	140(73.30)	76.621
≥ 40 Week to <52Week	0	0
Total	191(100)	97.051

***** Data is presented by interval and not cumulatively: minimum individual duration of exposure = 1 day; maximum individual duration of exposure = 232 days.

SIII.2 By Age Group and Gender

Total population (N=191)				
Age group (years)	**Persons (%)**		**Person time (person-years)**	
	M (%)	F (%)	M	F
<40	51(42.15)	34(48.57)	27.283	17.065
40 to 64	63(52.07)	30(42.86)	31.841	14.056
65 to 74	7(5.78)	6(8.57)	3.806	3.001
75 to 84	0	0	0	0
≥85	0	0	0	0
Total	121(100)	70(100)	62.930	34.122

SIII.3 By Dose

Total population (N=191)		
Dose of exposure	**Persons (%)**	**Person time (person-years)**
45 mg	151(79.06)	76.460
90 mg	40(20.94)	20.591

Total	191(100)	97.051

SIII.4 By Ethnic or Racial Origin

Total population (N=191)		
Ethnic/racial origin	**Persons (%)**	**Person time**
Multiple	0	0
Asian	0	0
Black or African American	1(0.52)	0.542
White	190(99.48)	96.509
Other	0	0
Total	191(100)	97.051

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

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

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Criterion 1	**Patient has a history of hypersensitivity to any biologic systemic therapy or any of the excipients of Bmab 1200/Stelara®.**
Reason for being an exclusion criterion	Patients with a history of immediate hypersensitivity to an immunoglobulin product were excluded from Ustekinumab trials to avoid potentially life-threatening hypersensitivity reactions.
Included as missing information	No
Rationale (if not included as missing information)	Serious systemic hypersensitivity reactions are an important identified risk for Bmab 1200. It is not possible to predict which patients may develop a hypersensitivity reaction to Bmab 1200. Bmab 1200 is contraindicated in patients with a known hypersensitivity to the activate substance or to any of the excipients (SmPC section 4.3 [Contraindications]). Additional information regarding hypersensitivity reactions that occur during treatment with Bmab 1200 is provided in SmPC section 4.4 (Special Warnings and Precautions for Use).
Criterion 2	**Patient who has a current or past history of any of the infections (congenital or acquired immunodeficiency, hepatitis B virus (HBV) or hepatitis C virus (HCV), active tuberculosis (TB)**
Criterion 3	**Patient has an underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic including central nervous system demyelinating disease, endocrine, cardiac, infection, or gastrointestinal) which, in the opinion of the investigator, significantly immune compromises the patient and/or places**

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
	the patient at unacceptable risk for receiving an immunomodulatory therapy
Criterion 4	**Any recurrent bacterial, fungal, opportunistic, or viral infection including recurrent/disseminated herpes zoster that, based on the investigator´s clinical assessment, causes a safety risk and makes the patient unsuitable for the study.**
Reason for being an exclusion criterion	Treatment with immunomodulatory agents may increase the risk of infection or worsen an existing infection. The exclusion criterion related to herpes zoster was based on the potential safety concern of reactivation of zoster with treatment with a selective immunosuppressant
Included as missing information	No
Rationale (if not included as missing information)	Serious infections (including mycobacterial and salmonella infections) are an important potential risk for Bmab 1200. Bmab 1200 is contraindicated in patients with clinically important, active infection such as active TB (SmPC section 4.3 [Contraindications]). Clinical experience suggests the immunosuppression seen with ustekinumab is minimal; however, the SmPC notes that caution should be exercised when considering the use of ustekinumab in patients with a chronic infection or a history of recurrent infection. Bmab 1200 may have the potential to increase the risk of infections and reactivate latent infections (SmPC section 4.4 [Special Warnings and Precautions for Use]). Guidance for the management of subjects who develop infections while being treated with Bmab 1200 is provided in SmPC section 4.4 (Special Warnings and Precautions for Use). While herpes zoster has been recognized as an adverse drug reaction (ADR) for ustekinumab, there has been no evidence of clinically severe presentations, frequent dissemination, or increased reactivations in clinical experience.
Criterion 5	**Were pregnant, nursing, or planning pregnancy during the trial and for a specified time thereafter.**
Reason for being an exclusion criterion	Per ICH guidance, pregnant women are generally excluded from clinical trials. It is unknown whether ustekinumab is excreted in human milk.
Included as missing information?	No
Rationale (if not included as missing information)	<u>Exposure during pregnancy</u> Guidance for the use of Bmab 1200 during pregnancy

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
	is provided in the SmPC section 4.6 (Fertility, Pregnancy and Lactation). Neither routine nor additional pharmacovigilance activities have identified any safety signals associated with the use of reference product Stelara® during pregnancy. The Stelara® MAH considered that sufficient exposure data have been collected and does not consider exposure during pregnancy as missing information. Use during breast-feeding Guidance for the use of Bmab 1200 during breast-feeding is provided in the SmPC section 4.6 (Fertility, Pregnancy and Lactation).
Criterion 6	**Had a transplanted organ/tissue or stem cell transplantation.**
Reason for being an exclusion criterion	This is typical, prudent, precautionary position when a drug has not been widely used in humans. Most patients who have undergone organ transplant require immunosuppressant medications that preclude inclusion in clinical trials.
Included as missing information?	No
Rationale (if not included as missing information)	Transplant patients generally receive immunosuppressive therapy to prevent rejection of the transplanted organ. Exposure to ustekinumab might increase the risk of complications from concomitant immunosuppression. Summary of Product Characteristics section 4.4 (Special Warnings and Precautions for Use) notes that caution should be exercised when considering concomitant use of other immunosuppressants or when transitioning from other immunosuppressive biologics.
Criterion 7	**Had history of malignancy within 5 years except adequately treated cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma.**
Reason for being an exclusion criterion	Treatment with an immunomodulatory agent may theoretically increase the risk of developing a malignancy. However, even with potent immunosuppressive agents, a causal relationship between immunosuppression and malignancy has not been established. A theoretical risk was recognized based on nonclinical data demonstrating anti IL-12 activity in mice. Therefore, patients with malignancy were excluded.
Included as missing information?	No

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Rationale (if not included as missing information)	With the completion of C0168Z03 (PSOLAR) from the reference product Stelara®, all additional pharmacovigilance activities for missing information 'Use in patients with concurrent malignancy or a history of malignancy' have been completed. Use in these patients is no longer considered missing information. Risk management is adequately addressed through routine pharmacovigilance and routine risk minimization.
Criterion 8	**Having a Bacillus Calmette-Guérin (BCG) vaccination within 1 year before the baseline visit and must agree not to receive a BCG vaccination during the study and at least 1 year after the last dose of the study treatment.**
Reason for being an exclusion criterion	Administration of live vaccines during immunomodulatory therapy may increase the risk of active infection following vaccination
Included as missing information?	No
Rationale (if not included as missing information)	Clinical experience suggests the immunosuppression seen with Ustekinumab is minimal, however the SmPC recommends that before live viral or live bacterial vaccination, treatment with Bmab 1200 should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination (SmPC section 4.4 [Special Warnings and Precautions for Use]).
Criterion 9	**Had a severe progressive or uncontrolled, clinically significant disease that in the judgment of the investigator renders the patient unsuitable for the study.**
Reason for being an exclusion criterion	This is typical, prudent, precautionary position, applied to clinical trial subjects when a drug has not been widely used in humans.
Included as missing information?	No
Rationale (if not included as missing information)	The impracticalities of identifying adequate numbers of patients with progressive concomitant disease in each of these categories precludes the further study of Bmab 1200 in these patient populations. Given the severity of disease in subjects with severe, progressive, or uncontrolled hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, psychiatric, or cerebral disease, the risk-benefit balance of the use of Bmab 1200 should be carefully evaluated on a case-by-case basis.

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, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

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

Table 2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Women of childbearing potential had to be willing to use a reliable method of contraception throughout the study period in all studies with Biocon/Partners Ustekinumab, and women who (inadvertently) became pregnant had to discontinue the study. From the isolated occurrences of (unintended) pregnancies that were reported, there is no indication of a safety concern. 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. 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 of this is unknown, however, the risk of infection in infants exposed in utero to ustekinumab may be increased after birth. Administration of live vaccines (such as the BCG vaccine) to infants exposed in utero to ustekinumab is not recommended for 6 months following birth or until ustekinumab infant serum levels are undetectable. If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.
Breastfeeding women	There are no clinical trial data on use of ustekinumab in breast feeding women. Not included in the clinical development program. According to publicly available information, limited data from published literature suggests that ustekinumab is excreted in human breast milk in very small amounts. It is not known if ustekinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from ustekinumab, a decision on whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with ustekinumab must be made taking into account the benefit

Type of special population	Exposure
	of breast-feeding to the child and the benefit of ustekinumab therapy to the woman[3]
Children	There are no clinical trial data on use of Bmab 1200 in children. Based on the US reference product[3] Stelara®, the safety and effectiveness of Stelara® have been established in pediatric patients 6 to 17 years old with moderate to severe plaque psoriasis. Use of Stelara® in adolescents is supported by evidence from a multicenter, randomized, 60-week trial (Ps STUDY 3) that included a 12-week, double-blind, placebo-controlled, parallel-group portion, in 110 pediatric subjects 12 years and older Use of Stelara® in children 6 to 11 years with moderate to severe plaque psoriasis is supported by evidence from an open-label, single-arm, efficacy, safety, and pharmacokinetics study (Ps STUDY 4) in 44 subjects. The safety and effectiveness of reference product Stelara® for pediatric patients less than 6 years of age with psoriasis have not been established. The safety and effectiveness of Stelara® have not been established in pediatric patients with PsA, CD, or UC.
Elderly	There are no clinical trial data on use of Bmab 1200 in elderly. Based on the US reference product Stelara® post marketing data 6709 patients exposed to Stelara®, a total of 340 were 65 years or older (183 patients with psoriasis, 65 patients with PsA, 58 patients with Crohn's disease and 34 patients with UC), and 40 patients were 75 years or older. Although no overall differences in safety or efficacy were observed between older and younger patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Dedicated studies in people with renal or hepatic or cardiovascular impairment have not been carried out. And, clinical trials are not conducted in immunocompromised patients. Patients with a disease severity different from inclusion criteria in clinical trials were not included in the clinical development program.

Type of special population	Exposure
Population with a relevant different ethnic origin	The clinical development programme included mostly white patients. Few black or African American and Asian patients were studied. Although not systematically evaluated, no particular risk or safety concern specific to individuals of certain racial and/or ethnic origin were observed. There is also no indication for any safety concerns specific to patients of certain racial and/or ethnic origin from experience with the reference product Stelara®.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.

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

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

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

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

Part II: Module SV - Post-authorisation experience

Usrenty has not yet been authorised in any country worldwide. This module is not applicable.

SV.1 Post-authorisation exposure

Not applicable

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

SVI.1 Potential for misuse for illegal purposes

The product is restricted by prescription only. This is not a substance abuse drug and no potential for misuse of Usrenty ((biosimilar to Ustikenumab) for illegal purposes is foreseen.

No trials have been conducted to evaluate the dependence potential of ustekinumab. The available data suggest that ustekinumab is unlikely to cause dependence. As a class, therapeutic mAbs are not associated with dependence, and the chemical structure of ustekinumab differs from central nervous system-active drugs associated with dependence. The pharmaceutical and PK/pharmacodynamic characteristics of ustekinumab are not characteristic of drugs with high dependence potential (e.g., rapid onset/short-acting active substances). In repeated dose toxicology studies of reference product Stelara®, no abnormal behavior or withdrawal symptoms were observed following cessation of dosing in recovery periods.

Part II: Module SVII - Identified and potential risks

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

Usrenty is a biosimilar product to Stelara® (Janssen-Cilag International, NV). Therefore, the safety profile of Usrenty is based on the general safety profile of ustekinumab, which resulted from the extensive experience with Stelara® (date of authorisation in EU: 15-Jan-2009) but also considering the development programme for Usrenty. Nonetheless, the development programme for Usrenty, did not raise new safety concerns; all clinical relevant adverse effects reported in the respective clinical studies corresponded to the known safety profile of ustekinumab (for full information on reported adverse events within the clinical development programme for Usrenty, refer to - Section 2.5 Clinical Overview

On 15-Jan-2009, product Stelara®was authorised by the European Commission according to EMA product number- EMEA/H/C/000958. Accordingly, the safety concerns for Usrenty are based on the list of safety concerns as presented in the European Public Assessment Report (EPAR) for Stelara® published on 28-Feb-2024.

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

There are currently no risks considered as not important for inclusion in the list of safety concerns in respect to this RMP.

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

All safety concerns in the RMP for a biosimilar product Usrenty are solely based on the safety concerns for the reference medicinal product Stelara® containing ustekinumab.

Important identified risks

None

Important potential risks

1) Serious infections (including mycobacterial and salmonella infections)

Risk-benefit impact:

Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. In clinical studies and a post-marketing observational study in patients with psoriasis, serious bacterial, fungal, and viral infections have been observed in patients receiving reference product (EPAR Stelara®). Opportunistic infections including reactivation of tuberculosis, other opportunistic bacterial infections (including atypical mycobacterial infection, listeria meningitis, pneumonia legionella, and nocardiosis), opportunistic fungal infections, opportunistic viral infections (including encephalitis caused by herpes simplex 2), and parasitic infections (including ocular toxoplasmosis) have been reported in patients treated with ustekinumab. Caution should be exercised when considering the use of Usrenty in patients with a chronic infection or a history of recurrent infection. If a patient develops a serious infection, the patient should be closely monitored and Usrenty should not be administered until the infection resolves.

2) Malignancy

Risk-benefit impact:

Immunosuppressants like ustekinumab have the potential to increase the risk of malignancy. Some patients who received reference product (EPAR Stelara®) in clinical studies and in a post-marketing observational study in patients with psoriasis developed cutaneous and non-cutaneous malignancies. The risk of malignancy may be higher in psoriasis patients who have been treated with other biologics during the course of their disease. Caution should be exercised when considering the use of Usrenty in these patients. 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.

3) Cardiovascular events

Risk-benefit impact:

Cardiovascular events including myocardial infarction and cerebrovascular accident have been observed in patients with psoriasis exposed to reference product (EPAR Stelara®) in a post-marketing observational study. Risk factors for cardiovascular disease should be regularly assessed during treatment with Usrenty.

4) Serious depression including suicidality

Risk-benefit impact:

Psoriasis patients can have an increased risk for depression and, in rare cases, suicide. Depression has been identified as an ADR for reference product (EPAR Stelara®) based on a safety signal identified in the placebo-controlled period from the Phase 2 and Phase 3 psoriasis clinical trials of reference product. The incidence of serious depression including suicidality across indications remains low. The available safety data from clinical studies of Usrenty 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 Usrenty in line with reference product (EPAR Stelara®).

5) Venous thromboembolism

Risk-benefit impact:

Currently, there is no known mechanism by which Usrenty could induce or exacerbate Venous Thromboembolism (VTE). The available literature shows that IL-12 and IL-23 are not implicated in the process of venous thrombosis. However, patients with IBD are at higher risk of venous thrombosis. Venous thromboembolism in patients with IBD is a multifactorial event that involves both hereditary and acquired factors. The pathogenesis of thrombosis in IBD is complex and not fully known. In patients with IBD, several mechanisms triggered by active inflammation may contribute to a higher prothrombotic state.

Missing Information

- Long-term safety in pediatric psoriasis patients 6 years and older
- Long-term impact on growth and development in pediatric psoriasis patients 6 years and older
- Long-term safety in adult patients with moderately to severely active Crohn's disease

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

Not applicable; this is the initial RMP.

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

All the risks and missing information presented here in line with reference product Stelara® RMP[4] Version 30.1 Health Authority (EMA) approval dated 05 September 2024.

Important identified risks

None

Important potential risks

- Serious infections (including mycobacterial and salmonella infections)
- Malignancy
- Cardiovascular events
- Serious depression including suicidality
- Venous thromboembolism

Missing Information

- Long-term safety in pediatric psoriasis patients 6 years and older
- Long-term impact on growth and development in pediatric psoriasis patients 6 years and older
- Long-term safety in adult patients with moderately to severely active Crohn's disease

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

Important Identified Risk: None

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

Potential Mechanisms:

Studies performed in mice suggest that IL-12 may contribute to protective immune responses to intracellular protozoa, bacteria, and fungal pathogens (Trinchieri 2003)[11], and IL-23 may contribute to immunity to *Klebsiella pneumonia* (Happel 2005)[12], *Mycobacterium tuberculosis* (Khader 2005)[13], *Cryptococcus neoformans* (Kleinschek 2006)[14], and *Candida albicans* (AcostaRodriguez 2007)[15]. See also the discussion regarding infection in Module SII.

Humans who are genetically deficient for IL-12/23p40 or IL-12RP1 and who are presumed to be deficient in both IL-12 and IL-23 function have normal resistance to ubiquitous viruses and fungi, gram-positive and gram-negative bacteria, and common opportunistic protozoa. These individuals are susceptible to non-TB primary mycobacteria infection, including BCG, and recurring *Salmonella sp.* (Fieschi 2003); (Novelli 2004). Filipe-Santos et al (2006)[18] reviewed inborn errors of IL-12/23 and reported that these patients, when vaccinated with BCG, developed BCG disease. They also found that these patients were more susceptible to salmonella infections.

Evidence Source(s) and Strength of Evidence:

Published nonclinical and medical literature suggest that inhibition of IL-12/23 may predispose patients to serious infections. 'Serious infections (including mycobacterial and salmonella infections)' is considered an important potential risk with Usrenty based upon the theoretical risk identified from nonclinical data and in humans who are genetically deficient for the cytokines that are inhibited by Usrenty (IL-12/23p40 or IL-12RP1). However, the risk of

developing serious infections (including mycobacterial and salmonella infections) in subjects on anti-IL-12/23p40 therapy such as Usrenty is currently unknown.

Till DLP of this RMP preparation no serious infections reported from Usrenty clinical trials and current data does not suggest an increased risk of serious infection in the overall ustekinumab-treated population.

Characterization of the Risk:

Based on the review of the data till DLP of this RMP preparation, no new safety information was identified for the important potential risk of 'Serious infections (including mycobacterial and salmonella infections).'

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

Patients who develop infections may potentially have a more severe course due to use of an immunomodulating agent such as ustekinumab. This important potential risk needs to be carefully weighed against the benefit conferred by use of ustekinumab.

Risk Factors and Risk Groups:

Serious infections

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

TB

The most common risk factors for the development of TB include conditions impairing the development of effective cell-mediated immunity to the infection (i.e., 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 (i.e., 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 intra cellulare* complex (MAC) disease included male sex (OR=2.1; 95% CI 1.0 to 4.5) and age >50 years (OR=26.5; 95% CI 10.9 to 67.3; O'Brien 2000)[19]. Similarly, in a US study (Cassidy 2009)[20] including 933 patients with 1 or more NTM isolates, pulmonary disease prevalence was highest in persons aged >50 years (15.5 cases per 100,000 persons). In addition, chronic respiratory disease, especially chronic obstructive pulmonary disease treated with inhaled corticosteroid therapy is a strong risk factor for NTM pulmonary disease (Andrejak 2013)[21]. Prolonged occupational exposure to soil was an important risk factor for MAC infection in a US study (Reed 2006)[22].

Salmonella

Factors that could increase risk of salmonella infection include activities that result in close contact with salmonella (e.g., international travel, Owning, handling or petting animals) and health issues that weaken resistance to infection (e.g., stomach or bowel disorders leading to use of antacids; recent antibiotic use; inflammatory bowel disease (IBD); or impaired immunity from acquired immune problems examples include HIV/AIDS, Sickle cell disease, Malaria, Anti-rejection drugs taken after organ transplants and Corticosteroids use.) (Mayo Clinic 2022) [23].

Preventability:

Usrenty is contraindicated in patients with a clinically important, active infection (e.g., active TB) (SmPC section 4.3 [Contraindications]). To prevent serious infections, it is recommended that live vaccines not be given concurrently with Usrenty (SmPC sections 4.4 [Special Warnings and Precautions for Use] and 4.5 [Interaction with Other Medicinal Products and Other Forms of Interaction]). For infants exposed to ustekinumab in utero, administration of live vaccines is not recommended for 6 months following the birth or until ustekinumab infant serum levels are undetectable (SmPC sections 4.4 [Special Warnings and Precautions for Use], 4.5 [Interaction with Other Medicinal Products and Other Forms of Interaction], and 4.6 [Fertility, Pregnancy and Lactation]).

Serious infections

Caution should be exercised when considering the use of Usrenty 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 Usrenty should not be administered until the infection resolves.

Tuberculosis (TB)

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

Nontuberculous mycobacteria (NTM) infections

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

Salmonella

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

Impact on the Risk-Benefit Balance of the Product:

The available cumulative information does not provide evidence for an increased risk of serious infections in patients treated with ustekinumab and therefore a negative impact on the risk-benefit balance of the product is not evident.

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

Public Health Impact:

The potential public health impact is not known.

MedDRA Term search criterion:

SOC: Infections and infestations.

Important Potential Risk: Malignancy

Potential Mechanisms:

Scientific literature suggests that IL-12 can contribute to tumor immunosurveillance (Colombo 2002)[38] and exogenous IL-12 can promote tumor-directed cytotoxic T cell responses in tumor vaccine strategies. In contrast, IL-23 has been reported to promote tumor growth in animal models. The preponderance of evidence from the published literature (knockout models where IL-23 is ablated) suggests that a risk for malignancy may actually be reduced in the setting of IL-23 inhibition. However, conflicting data from a limited number of studies in mouse models and from photocarcinogenicity experiments point to an increased risk of malignancy in IL-23p 19-deficient mice exposed to UVB radiation. Existing data provide evidence to support an association between impaired IL-12 and/or IL-23 signalling and both tumor growth and resistance to tumor growth, although the nature of these relationships is not fully understood. Long-term post marketing safety evaluations of agents targeting IL-12/23 and IL-23 are needed to fully appreciate the associated malignancy risk. The implications for therapeutic inhibition of IL-12/23 or IL-23 remain uncertain. (Elizabeth N. Ergen, 2018)[24]

Evidence Source(s) and Strength of Evidence:

Immunosuppressants like ustekinumab have the potential to increase the risk of malignancy[3]. In the pooled controlled portion of clinical trials across indications, the rate of malignancy other than non-melanoma skin cancer was low and was balanced between the ustekinumab and comparator groups.

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

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

Characterization of the Risk:

Based on the review of the data from Usrenty clinical trials, no new safety information was identified for the important potential risk of 'Malignancy.' As noted above, the incidence of malignancy in ustekinumab clinical trials was consistent with that in the general population.

From the Usrenty clinical trials there are 3 events reported with the events of Malignancy.

From the Phase 1 study, one Subject received 45 mg Usrenty in the study and reported an SAE of severe tonsil cancer on Day 26. The investigator assessed this event as unlikely related to the study drug considering its size at the time of diagnosis. It was certainly present at screening or Day -1 but small enough to go unnoticed at that time. This event did not result in the discontinuation of the subject from the study and was considered ongoing at the time of study completion.

From the Phase 3 study,

one patient had received 45 mg of Usrenty in the study and reported SAE of endometrial adenocarcinoma on Day 22. The event was resolved on Day 30. The Investigator assessed the SAE as unrelated to the study drug since the subject already had a history of abnormal bleeding from genital tract prior to dosing. The alternate causality was reported as pre-existing abnormal bleeding from the genital tract.

Another patient had received 90 mg of Usrenty in the study and reported SAE of squamous cell carcinoma of the tongue on Day 30. The event was resolved on Day 238. The investigator assessed event as unlikely related to study treatment. The alternate causality was reported as chronic irritation with denture for 15 years (last replaced 3 years ago).

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

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

Risk Factors and Risk Groups:

Among psoriasis patients, increased risk of solid cancers appears to be related to alcohol drinking and cigarette smoking. In addition, exposure to PUV A and immunosuppressants, including cyclosporin and possibly MTX, has been associated with squamous cell carcinoma in psoriasis patients (Pouplard 2013)[25]. General risk factors for malignancy include increasing age, lifestyle factors (such as use of alcohol and tobacco and obesity), family history of cancer, and certain environmental exposures.

Risk factors for the development of malignancy can differ by cancer site. However, in general, factors that can increase risk of malignancies in IBD patients include but are not limited to smoking, ongoing inflammation, and carcinogenic effects of immunosuppressive drugs.

Preventability:

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

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

Impact on the Risk-Benefit Balance of the Product:

Although malignancies have been reported in patients treated with ustekinumab in clinical trials and in the post marketing setting from reference product Stelara®, available cumulative information does not suggest an increased risk of malignancy in patients treated with ustekinumab. Therefore, no negative impact on the risk-benefit balance of the product is evident.

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

Public Health Impact:

The potential public health impact is not known.

MedDRA Term search criterion:

SMQ: Malignant tumours (narrow).

Important Potential Risk: Cardiovascular Events

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 or mild psoriasis (Neimann 2006)[26]. The greatest risk of myocardial infarction (MI) is found in young patients with severe psoriasis (Gelfand 2006)[26]. As in psoriasis, patients with PsA are reported to be at increased risk for occlusive vascular diseases, including MI and stroke (Tobin 2010)[27]; (Gladman 2009)[28]. The potential mechanistic link between psoriasis and CV events, if any, is unclear.

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

Evidence Source(s) and Strength of Evidence:

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

A numeric imbalance in rates of investigator-reported major adverse cardiovascular events (MACE) was observed between reference product Stelara® and placebo-treated subjects in the controlled portions of Phase 2 and Phase 3 trials in psoriasis, resulting predominantly from an imbalance in event rates from a smaller Phase 2 trial. Additional analyses performed internally by the reference product Stelara® MAH show that the overall rates of MI and stroke with up to 5 years of treatment with Stelara® in psoriasis patients are comparable with expected rates in either the general population or in the psoriasis population, and comparable to rates in trials of other biologics.

Through approximately 5 years of follow-up in CD clinical trials and approximately 4 years of follow-up in UC clinical trials, the incidence of serious MACE was low in ustekinumab-treated subjects and placebo-treated subjects, with no consistent evidence that ustekinumab increases cardiovascular risk. Across indications, analysis of MACE in controlled portions of the pooled clinical trial data of reference product Stelara® does not currently suggest a significant increased risk of MACE in subjects treated with ustekinumab.

In summary, the totality of the currently available data does not suggest that Ustekinumab increases the risk of MACE. However, in light of the imbalance of CV events in the short-term,

placebo-controlled portions of the psoriasis clinical trials and the known increased risk of these events in the psoriasis and PsA populations, CV events are considered an important potential risk for ustekinumab.

Characterization of the Risk:

From the available clinical trial data of Usrenty, no new safety information was identified for the important potential risk of 'Cardiovascular events.'

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

Risk Factors and Risk Groups:

Risk factors for the development of CV disease are well known and include hypertension, hypercholesterolemia, diabetes, smoking, age, male sex, obesity, and family history. (Ferraz 2020)[29].

Preventability

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

Impact on the Risk-Benefit Balance of the Product:

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

Public Health Impact:

The potential public health impact is not known.

MedDRA Term search criterion:

SOC: Cardiac disorders.

Important Potential Risk: Serious Depression Including Suicidality

Potential Mechanisms:

Depression is a complex disease with a variety of biologic theories for the pathophysiology. The mechanism by which Usrenty could cause depression is not known.

Evidence Source(s) and Strength of Evidence:

Psoriasis patients can have an increased risk for depression and, in rare cases, suicide. Depression has been identified as an ADR for Usrenty (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 reference product Stelara®. The incidence of serious depression, including suicidality across indications, remains low.

The available safety data from clinical studies 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 Usrenty.

Characterization of the Risk:

Based on the review of the Clinical data to date, no new safety information was identified for the important potential risk of 'Serious depression including suicidality.' No safety signal has been observed.

The impact of depression on the individual patient may be very significant, and patients with a history of untreated or inadequately treated depression should be treated for such. There may be psychosocial impact and possibility of death from suicide attempts.

Risk Factors and Risk Groups:

Risk factors for depression include older age and associated neurological conditions; uncontrolled, poorly treated psoriasis; recent childbirth; stressful life events; a personal or family history of depression; and selected medical comorbid conditions including psoriatic conditions and IBD. Suicide rates are twice as high in families of suicide victims (Jang J 2022)[39].

Preventability:

There is no known means of preventing depression.

Impact on the Risk-Benefit Balance of the Product:

Although depression has been reported in patients treated with reference product Stelara® in clinical trials and in the post marketing setting, available cumulative information does not provide evidence for an increased risk of depression in patients treated with ustekinumab. Therefore, no significant negative impact on the risk-benefit balance of the product is evident.

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

Public Health Impact:

The potential public health impact is not known.

MedDRA Term search criterion:

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

Important Potential Risk: Venous Thromboembolism

Potential Mechanisms:

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

However, patients with Inflammatory bowel disease (IBD) are at higher risk of venous thrombosis. Venous thromboembolism in patients with IBD is a multifactorial event that involves both hereditary (factor V Leiden mutation, G2021 0A mutation of the prothrombin gene, and homozygous C677T mutation in the methylenetetrahydrofolate reductase gene) and acquired factors (dehydration, indwelling catheters, prolonged immobilization, hyperhomocysteinemia, surgical interventions, active disease with a high inflammatory burden, hospitalization, colonic localization, recent surgery, oral contraceptive use, etc).

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

- Increased plasma levels of recognized risk factors for thrombosis (e.g., TNFa, IL-6, and IL-8 levels, several of which are also considered to be acute-phase reactant) and decreased levels of natural anticoagulants

- Reduced fibrinolytic activity

- Endothelial abnormalities that are mainly represented by the downregulation of the anticoagulant thrombomodulin and endothelial protein C receptor, which in turn affects the conversion of protein C into its activated form

- Abnormalities of platelets, such as thrombocytosis and increased activation and aggregation (Papa 2014)[30].

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

Evidence Source(s) and Strength of Evidence:

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

Venous thromboembolism was originally identified as an important potential risk based on data collected through 44 weeks of treatment in the ustekinumab CD clinical trials. Through approximately 5 years of follow-up in CD clinical trials and approximately 4 years of follow-up in UC clinical trials, while there is a slight imbalance across treatment groups in the reporting of all vascular thrombotic events, the overall incidences per 100 subject-years (~0.1 [~1 %]) observed among Stelara®-treated subjects in both the CD and UC populations are within the range of 1 % to 8% reported in the IBD literature {(Alkim 2017)[35]; (Danese 2007)[36]; (Nguyen 2014)[37]}.

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

Characterization of the Risk:

The impact of VTE on the individual patient may be significant and may result in a fatal outcome or cause serious long-term complications.

Patients with IBD may require prolonged or indefinite anticoagulant therapy. Patients may experience debilitating VTE events including events of deep vein thrombosis, pulmonary embolism, or splanchnic vein thrombosis with or without fatal outcome. The occurrence of VTE imparts a greater risk of in-hospital mortality among hospitalized IBD patients that is greater

than the greater mortality risk imparted by VTE in the non-IBD population (Nguyen 2014)[37]. Patients with IBD require vigilance in adequate treatment of VTE risk factors.

Risk Factors and Risk Groups:

Patients suffering from IBD, namely CD and UC, are more prone to thromboembolic complications compared with the general population (Zezos 2014)[31].

A study of IBD patients conducted in the UK reported that there was an increased risk of VTE during disease flares and chronic activity (Grainge 2010)[32]. In a Danish population study that included children and adults, the highest risk of VTE was in the 0 to 20 years age group with an HR of 6.6 (95% CI 3.3 to 13.2) compared with 1.6 (95% CI 1.5 to 1.8) for the 2:60 years age group (Kappelman 2011)[33]. The risk has also been reported to be greater for males (incidence rate of 1.34 per 1,000 PY) than for females (incidence rate of0.73 per 1,000 PY). Smoking and the need for steroid treatment have also been shown to be risk factors for VTE with ORs of 3.46 (95% CI 1.14 to 10.5) and 2.97 (95% CI 0.99 to 8.92), respectively (Vegh 2015)[34].

Preventability:

Patients with risk factors for venous thrombosis may require prophylactic anticoagulation. Preventability is also aimed at reducing acquired risk factors through appropriate measures like providing adequate hydration, effective anti-inflammatory treatment, early mobilization after surgery, graduated compression stockings or pneumatic devices, limited and rational use of venous catheters, weight loss, alternative methods of contraception, etc.

Impact on the Risk-Benefit Balance of the Product:

Although VTE has been reported in patients treated with ustekinumab in clinical trials and in the postmarketing setting, available cumulative information does not provide evidence for causal association between VTE and the use of ustekinumab. Therefore, no significant negative impact on the risk-benefit balance of the product is evident.

Further characterization of the incidence, risk factors, and potential relationships with the use of ustekinumab for VTE is conducted through routine pharmacovigilance activities, clinical trials, and epidemiological study.

Public Health Impact:

The potential public health impact is not known.

MedDRA Term search criterion:

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

SVII.3.2. Presentation of the Missing Information

Missing information: Long-term safety in pediatric psoriasis patients 6 years and older
Evidence source: This missing information is based on the safety profile of ustekinumab as reflected in the reference product information for Usrenty/Stelara® and summary of safety concerns published in EPAR for Stelara®. The MAH of Stelara® conducting trials CNTO1275PSO3006 and CNTO1275PSO3013 investigated the use of ustekinumab in pediatric psoriasis patients 6 years and older through 60 weeks and 176 weeks, respectively. A relatively small number of pediatric subjects ≥6 to <18 years of age (71 male and 83 female) were exposed to ustekinumab in the pediatric psoriasis clinical trials

Population in need of further characterization: Pediatric patients with psoriasis ≥ 6 years of age with long-term exposure to Usrenty.

Missing information: Long-term impact on growth and development in pediatric psoriasis patients 6 years and older
Evidence source: This missing information is based on the safety profile of ustekinumab as reflected in the reference product information for Usrenty/Stelara® and summary of safety concerns published in EPAR for Stelara®. The MAH of Stelara® conducting trials CNTO1275PSO3006 and CNTO1275PSO3013 investigated the use of ustekinumab in pediatric psoriasis patients 6 years and older through 60 weeks and 176 weeks, respectively. A relatively small number of pediatric subjects ≥6 to <18 years of age (71 male and 83 female) were exposed to ustekinumab in the pediatric psoriasis clinical trials
Population in need of further characterization: Pediatric patients with psoriasis ≥6 years of age with long-term exposure to Usrenty.

Missing information: Long-term safety in adult patients with moderately to severely active Crohn's disease
Evidence source: This missing information is based on the safety profile of ustekinumab as reflected in the reference product information for Usrenty/Stelara® and summary of safety concerns published in EPAR for Stelara®. The MAH of Stelara® conducting trials CNTO1275CRD3001, CNTO1275CRD3002, and CNTO1275CRD3003 investigated the use of Ustekinumab in adult CD from the first dose of Ustekinumab through Week 272. The MAH of Stelara® also conducting RRA-20745, an observational PASS, monitored the long-term safety profile of ustekinumab in adult patients with moderately to severely active CD.
Population in need of further characterization: Adults with moderately to severely active CD who have been treated with Usrenty long-term. The MAH of Stelara® conducting a PASS using Swedish Nationwide Healthcare Registers and the independent Swedish National Quality Register for Inflammatory Bowel Disease (SWIBREG; PCSIMM002807) to characterize the long-term safety profile of Stelara® in adult patients with moderately to severely active CD is ongoing.

Part II: Module SVIII - Summary of the safety concerns

The identified and potential risks historically known with ustekinumab are discussed below in the light of experience gained with the reference product (Stelara®).

Table 2: 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
Missing information	• Long-term safety in pediatric psoriasis patients 6 years and older • Long-term impact on growth and development in pediatric psoriasis patients 6 years and older • Long-term safety in adult patients with moderately to severely active Crohn's disease

Note: ' Long-term safety in adult patients with moderately to severely active ulcerative colitis' is not considered for Usrenty because ulcerative colitis is not proposed indication for Usrenty

Part III: Pharmacovigilance Plan

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond 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	TOIQ to collect information on venous thromboembolism

Traceability:

Biocon Biologics acknowledges the need for traceability to be fully integrated in different healthcare settings and that infrastructure may vary between countries. A key requirement for pharmacovigilance of biologicals is the need to ensure continuous product and batch traceability in the clinical use. Communication should emphasize the importance of providing the product name (or INN and the name of marketing authorization holder) and the batch number(s) when reporting suspected adverse reactions. In line with international guidance on biological medicinal products, reporting drug name and batch number is mentioned in appropriate sections of Biocon Biologics Ustekinumab product information/labels and included in the product packaging. This information is therefore available to be recorded and reported at all levels in the supply chain from the manufacturer release to prescription, dispensing and patient information.

Ustekinumab will mainly be supplied in the hospital setting. A statement is presented in the product information/label reminding Healthcare Professionals (HCPs) on the type of the medicinal product (Biosimilar) and the need to clearly record both, the trade name and batch number in the patient's healthcare records. For the Biocon Biologics Ustekinumab biosimilar, in all countries, no matter if middle or low income, INN and batch number can be found on the package.

According to international guidelines for the use of Biosimilars, Biocon Biologics has a process in place to cover the requirements of traceability. Pharmacovigilance activities of biosimilar Ustekinumab follow established standard procedures laid down by Biocon Biologics to collect initial and follow up information. If any missing batch number or product name in the initial report received, then separate follow up will be made to the reporter. Adequacy of the data and proper assessment will be ensured. Biocon Biologics performs diligent follow up on national level to obtain trade name and batch number to distinguish the reports of the Biocon Biologics products to identify batch-related issues and product specific safety concerns.

Other Forms of Routine Pharmacovigilance Activities			
Activity	**Safety Concern(s)**	**Objective/Description**	**Milestones**

For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible.	All safety concerns	To monitor if there are any batch-specific issues in the post marketing environment.	Not applicable

III.2 Additional pharmacovigilance activities

As current routine pharmacovigilance activities are sufficient, no additional pharmacovigilance activities are recommended.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable, as routine pharmacovigilance only is proposed and there are no studies or other additional activities from the pharmacovigilance plan, whether ongoing, planned or completed.

Part IV: Plans For Post-Authorisation Efficacy Studies

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

Not applicable.

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

V.1. Routine Risk Minimisation Measures

Table 3: Description of routine risk minimization measures by safety concern.

Safety concern	Routine risk minimization activities
Serious infections (including mycobacterial and salmonella infections)	**Routine risk communication:** SmPC sections 4.3 (Contraindications), 4.4 (Special Warnings and Precautions for Use), 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction), 4.6 (Fertility, Pregnancy and Lactation), and 4.8 (Undesirable Effects) PL sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC section 4.4 (Special Warnings and Precautions for Use) • Guidance regarding evaluation of patients for TB infection, treatment of latent TB, and administration of anti-TB therapy in patients with a history of latent or active TB prior to initiation of Usrenty. • Recommendation to monitor patients for signs and symptoms of active TB during and after Usrenty 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 Usrenty.

	Other routine risk minimization measures beyond the Product Information: Legal status: Restricted medical prescription.
Malignancy	**Routine risk communication:** SmPC sections 4.4 (Special Warnings and Precautions for Use) and 4.8 (Undesirable Effects) PL section2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC section 4.4 (Special Warnings and Precautions for Use) • Guidance for monitoring patients for the appearance of skin cancer. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Cardiovascular events	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Serious depression including suicidality	**Routine risk communication:** SmPC section 4.8 (Undesirable Effects) PL section4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Venous thromboembolism	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None

	Other routine risk minimization measures beyond the Product Information: Legal status: Restricted medical prescription.
Long-term safety in pediatric psoriasis patients 6 years and older	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Long-term safety in adult patients with moderately to severely active Crohn's disease	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.

V.2. Additional Risk Minimisation Measures

None Planned.

V.3 Summary of risk minimisation measures and Pharmacovigilance Activities

Table 4: Summary table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety concern	**Routine risk minimisation measures**	**Pharmacovigilance Activities**

Serious infections (including mycobacterial and salmonella infections)	**Routine risk minimization measures:** • SmPC sections 4.3 (Contraindications), 4.4 (Special Warnings and Precautions for Use), 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction), 4.6 (Fertility, Pregnancy and Lactation), and 4.8 (Undesirable Effects) • PL sections 2 and 4 **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQs for serious infections and TB **Additional pharmacovigilance activities:** None
Malignancy	**Routine risk minimization measures:** • SmPC sections 4.4 (Special Warnings and Precautions for Use) and 4.8 (Undesirable Effects) • PL section 2 **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQs **Additional pharmacovigilance activities:** None
Cardiovascular events	**Routine risk minimization measures:** None **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQs **Additional pharmacovigilance activities:** None

Serious depression including suicidality	**Routine risk minimization measures:** • SmPC section 4.8 (Undesirable Effects) • PL section 4 **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Venous thromboembolism	**Routine risk minimization measures:** None **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOIQ **Additional pharmacovigilance activities:** None
Long-term safety in pediatric psoriasis patients 6 years and older	**Routine risk minimization measures:** None **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	**Routine risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

	Other routine risk minimization measures beyond the Product Information: • Prescription only medicine. **Additional risk minimization measures:** None	**Additional pharmacovigilance activities:** None
Long-term safety in adult patients with moderately to severely active Crohn' s disease	**Routine risk minimization measures:** None **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine. **Additional risk minimization 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 Usrenty (ustekinumab).

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

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

This summary of the RMP for Usrenty (ustekinumab) should be read in the context of all the 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 Usrenty (ustekinumab)'s RMP.

I. The medicine and what it is used for

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

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

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

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

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

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

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

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

II.A List of important risks and missing information

Important risks of Usrenty are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered.

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

Table 5: Summary of safety concerns

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

II.B Summary of important risks

Table 6: Important Potential Risk: Serious infections (including mycobacterial and salmonella infections)

Important Potential Risk: Serious infections (including mycobacterial and salmonella infections)	
Evidence for linking the risk to the medicine	Published nonclinical and medical literature suggest that inhibition of risk to the medicine interleukin (IL)-12/23 may predispose patients to serious infections. 'Serious infections (including mycobacterial and salmonella infections)' is considered an important potential risk with Usrenty based upon the theoretical risk identified from reference product Stelara® nonclinical data and in humans who are genetically deficient for the cytokines that are inhibited by Usrenty (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 Usrenty is currently unknown.

	Across clinical trials in all indications for which 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-tumor necrosis factor (TNF)s, other immunosuppressants, or other biologics. *Tuberculosis (TB)* The most common risk factors for the development of TB include conditions impairing the development of effective cell-mediated immunity to the infection (i.e., advanced age, human immunodeficiency virus [HIV] infection), alcohol abuse, malignancy, corticosteroids or other immunosuppression, connective tissue disease, renal failure, diabetes, and pregnancy. A risk factor for the development of TB is exposure to TB, and patients who were born or lived in countries considered by the World Health Organization to have a high TB burden (incidence: >300 TB cases/100,000 population/year) or have travelled to these locations may be at higher risk. Exposure in the health care setting or in high-density institutions (i.e., prisons) may also put patients at higher risk of development of TB. The possibility of latent TB must be considered, especially in patients who have immigrated from or travelled to countries with a high prevalence of TB or had close contact with a person with active TB. In patients who are severely ill or immunocompromised, tuberculin tests may yield false negative results. *Non-TB mycobacterial (NTM) infections* A retrospective/prospective review performed in Australia, found that significant risks for non-HIV-associated pulmonary Mycobacterium avium/Mycobacterium intracellulare complex (MAC) disease included male sex (odds ratios [OR]=2.1; 95% confidence interval [CI] 1.0 to 4.5) and age >50 years (OR=26.5; 95% CI 10.9 to 67.3). Similarly, in a United States (US) study including 933 patients with 1 or more NTM isolates, pulmonary disease prevalence was highest in persons aged >50 years (15.5 cases per 100,000 persons). In addition, chronic respiratory disease, especially chronic obstructive pulmonary disease treated with inhaled corticosteroid therapy is a strong risk factor for NTM pulmonary disease. 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 (e.g., international travel, owning a pet bird or reptile) and health issues that weaken resistance to infection (e.g.,

	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, antirejection drugs taken after organ transplants, and corticosteroids).
Risk minimization measures	Routine risk minimization measures: • SmPC sections 4.3 (Contraindications), 4.4 (Special Warnings and Precautions for Use), 4.5 (Interaction with Other Medicinal Products and Other Forms of interaction), 4.6 (Fertility, Pregnancy and Lactation), and 4.8 (Undesirable Effects) • Package Leaflet sections 2 and 4 • Prescription only medicine Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table 7: Important Potential Risk: Malignancy

Important Potential Risks: Malignancy	
Evidence for linking the risk to the medicine	There is a theoretical risk of malignancy associated with administration of risk to the medicine Ustekenumab based on scientific literature pertaining to inhibition of IL-12/23. In the pooled controlled portion of clinical trials across indications, the rate of malignancy other than non-melanoma skin cancer (NMSC) was low and was balanced between the ustekinumab and comparator groups. Because malignancies tend to take a long time to develop, long-term follow-up is most relevant. In psoriasis patients treated for up to 5 years of continuous reference product Stelara® therapy, the risk of malignancies other than NMSC was not increased compared with the general US population. There was no evidence of an increased risk of malignancy through approximately 5 years of follow-up in CD patients and approximately 4 years of follow-up in UC patients treated with Stelara®. Long-term effects of ustekinumab 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 groups related to alcohol drinking and cigarette smoking. In addition, exposure to psoralen and

	ultraviolet A and immunosuppressants, including cyclosporin and possibly methotrexate (MTX), has been associated with squamous cell carcinoma in psoriasis patients. General risk factors for malignancy include increasing age, lifestyle factors (such as use of alcohol and tobacco and obesity), family history of cancer, and certain environmental exposures. Risk factors for the development of malignancy can differ by cancer site. However, in general, factors that can increase risk of malignancies in IBD patients include but are not limited to smoking, ongoing inflammation, and carcinogenic effects of immunosuppressive drugs.
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.4 (Special Warnings and Precautions for Use) and 4.8 (Undesirable Effects) • Package Leaflet section 2 • Prescription only medicine Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table 8: Important potential Risk: Cardiovascular events

Important Potential Risk: Cardiovascular events	
Evidence for linking the risk to the medicine	The risk of developing cardiovascular (CV) events in subjects on anti-IL-12/23p40 therapy such as Ustekinumab is currently unknown. A numeric imbalance in rates of investigator-reported major adverse cardiovascular events (MACE) was observed between reference product Stelara®- and placebo-treated subjects in the controlled portions of Phase 2 and Phase 3 trials in psoriasis, resulting predominantly from an imbalance in event rates from a smaller Phase 2 trial. Additional analyses performed internally by the Marketing Authorization Holder show that the overall rates of myocardial infarction and stroke with up to 5 years of treatment with Stelara® in psoriasis patients are comparable with expected rates in either the general population or in the psoriasis population, and comparable to rates in trials of other biologics. Through approximately 5 years of follow-up in CD clinical trials and approximately 4 years of follow-up in UC clinical trials, the incidence of serious MACE was low in ustekinumab-treated subjects and placebo-treated subjects, with no consistent evidence that ustekinumab increases cardiovascular risk. Across indications, analysis of MACE in controlled portions of the

	pooled clinical trial data does not currently suggest a significant increased risk of MACE in subjects treated with ustekinumab. In summary, the totality of the currently available data does not suggest that ustekinumab increases the risk of MACE; however, in light of the imbalance of CV events in the short-term placebo-controlled portions of the psoriasis clinical trials and the known increased risk of these events in the psoriasis and PsA populations, CV events are considered an important potential risk for ustekinumab.
Risk factors and risk groups	Risk factors for the development of CV disease are well known and groups include hypertension, hypercholesterolemia, diabetes, smoking, age, male sex, obesity, and family history. The PsA, psoriasis, and CD populations share certain risk factors, such as increased CV risk, increased body weight, and increased body mass index.
Risk minimisation measures	Routine risk minimisation measures: In SmPC section 4.4 contains the relevant text regarding safety concerns. • Package Leaflet section 2 • Prescription only medicine Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table 9: Important potential risks: Serious depression including suicidality

Important potential risks: Serious depression including suicidality	
Evidence for linking the risk to the medicine	Psoriasis patients can have an increased risk for depression and, in rare cases, suicide. Depression has been identified as an ADR for Usrenty (SmPC section 4.8 [Undesirable Effects] and Package Leaflet section 4) based on a safety signal identified in the placebo-controlled period from the Phase 2 and Phase 3 psoriasis clinical trials. The incidence of serious depression including suicidality across indications remains low. The available safety data from clinical studies and postmarketing experience have not identified a safety signal of suicidal ideation or suicidal attempt (including completed suicide). However, based on the severity of these events, serious depression including suicidality is considered an important potential risk for Usrenty.
Risk factors and risk groups	Risk factors for depression include older age and associated neurological groups 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 minimization measures: • SmPC section 4.8 (Undesirable Effects) • Package Leaflet section 4 • Prescription only medicine Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table 10: Important potential risks: Venous thromboembolism

Important potential risk: Venous thromboembolism	
Evidence for linking the risk to the medicine	Patients with IBD can have an increased risk for blood clots in veins due to risk to the medicine their underlying condition and other risk factors (dehydration, use of catheters, prolonged immobilization, hospitalization, surgical interventions, oral contraceptive use, etc). Venous thromboembolism (VTE) was originally identified as an important potential risk based on data collected through 44 weeks of treatment in the Ustekinumab CD clinical trials. Through approximately 5 years of follow-up in CD clinical trials and approximately 4 years of follow-up in UC clinical trials, while there is a slight imbalance across treatment groups in the reporting of all vascular thrombotic events, the overall incidences per 100 subject-years (~0.1 [~ 1 %]) observed among 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 clinical trials through Week 220, and clinical trials conducted for other indications, as well as cumulative post marketing data, do not indicate an increased rate with Ustekinumab treatment.
Risk factors and risk groups	Patients suffering from IBD, namely CD and UC, are more prone to groups thromboembolic complications compared with the general population. A study of IBD patients conducted in the United Kingdom reported that there was increased risk of VTE during disease flares and chronic activity. In a Danish population study that included children and adults, the highest risk of VTE was in the 0 to 20 years age

	group with a hazard ratio of 6.6 (95% CI 3.3 to 13.2), compared with 1.6 (95% CI 1.5 to 1.8) for the ≥ 60 years age group. The risk has also been reported to be greater for males (incidence rate of 1.34/1000 person-years [PY]) than for females (incidence rate of 0.73/1000 PY). Smoking and the need for steroid treatment have also been shown to be risk factors for VTE with ORs of 3.46 (95% CI 1.14 to 10.5) and 2.97 (95% CI 0.99 to 8.92), respectively.
Risk minimization measures	Routine risk minimization measures: None Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

II.C Post-authorisation development plan

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

There are no studies, which are conditions of the marketing authorization or specific obligation of Usrenty.

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

Not applicable

Part VII: Annexes

List of Annexes

Annex 4 - Specific adverse event follow-up forms

Annex 6 - Details of proposed additional risk minimisation measures (if applicable)

Annex 4 - Specific adverse drug reaction follow-up forms

Table of Contents

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

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

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

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

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

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

Biocon Biologics
Transforming Healthcare. Transforming Lives.

TARGETED FOLLOW UP FORM- SERIOUS INFECTIONS AND OPPORTUNISTIC INFECTIONS
BBL Case No.:

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

Manufacturer Control Number: Drug generic (TRADENAME):

Date of Report: [dd-MMM-yyyy]

1. Medical History and Concurrent Conditions

☐ Prior history of exposure to TB

Details

☐ Prior history of exposure to Hepatitis B/C

Details:

Details of vaccination history:

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

Details:

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

2. Adverse Event Details

☐ The infection was present prior to starting the product

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

Details:

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

TARGETED FOLLOW UP FORM- TUBERCULOSIS (TB)
BBL Case No.:

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

Manufacturer Control Number: Drug generic (TRADE) Name:

Date of Report [dd-MMM-yyyy]

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

□ Weight loss ≥ 10% of ideal body weight	□ 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:

TARGETED FOLLOW UP FORM- TUBERCULOSIS (TB)
BBL Case No.:

☐ 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)		
PCRMTb			
Quantiferon TB Gold			

TARGETED FOLLOW UP FORM- MALIGNANCIES (INCLUDING LYMPHOMA, SECOND AND SECONDARY MALIGNANCIES)
BBL Case No.:

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

Manufacturer Control Number: Drug generic (TRADENAME):

Date of Report [dd-MMM-yyyy]

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

☐ Previous malignancy (Provide specific diagnosis):

☐ Occupational/Exposure history:

☐ Excessive sun exposure (Describe):

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

☐ History of radiation

Dose of radiation:

Area treated

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

Indication for radiation:

Any radiation induced changes?

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

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

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

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

☐ In first degree relatives:

☐ In more distant relatives:

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

Age at first exposure to any TNF blocker

TARGETED FOLLOW UP FORM- MALIGNANCIES (INCLUDING LYMPHOMA, SECOND AND SECONDARY MALIGNANCIES)
BBL Case No.:

☐ 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 Start Administration	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

TARGETED FOLLOW UP FORM- MALIGNANCIES (INCLUDING LYMPHOMA, SECOND AND SECONDARY MALIGNANCIES)
BBL Case No.:

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

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

(Ref. https://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm- Adverse Event Reporting Guidance/Forms)

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

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

3. Treatment

What was the response to the first treatment for malignancy?

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

TARGETED FOLLOW UP FORM- CARDIOVASCULAR EVENTS
BBL Case No.:

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

Manufacturer Control Number: Drug generic (TRADE) Name:

Date of Report [dd-MMM-yyyy]

1. Drug Details:

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

Recent **dose change? Details:**

When did the patient **last** receive the product **before the current dose?**

Date: [dd-MMM-yyyy], Time:

Date and time of dose (e.g., injections, infusions) **after which this** cardiovascular event occurred:

Date: [dd-MMM-yyyy], Time:

Date and time of onset of cardiovascular event **reported now**:

Date: [dd-MMM-yyyy], Time:

2. Relevant medical history (Provide prior diagnoses relevant laboratory data {including echo and

ischemic evaluation], dates, etc. below.)

□ Hypertension
□ Hyperlipidemia/Hypercholesterolemia/Hypertriglyceridemia
□ Obesity
□ Coronary artery disease
□ Myocardial infarction
□ Valvular heart disease
□ History of percutaneous coronary intervention
□ Coronary artery bypass graft
□ Congenital heart disease
□ Arrhythmias
□ Cardiomyopathy
□ Pericarditis
□Congestive heart failure
□ Peripheral artery disease

TARGETED FOLLOW UP FORM- CARDIOVASCULAR EVENTS
BBL Case No.:

□ Diabetes mellitus
□ Renal impairment
□ Liver disease
□ Headaches
□ Head trauma
□ Transient ischemic attack
□ Ischemic cerebrovascular accident
□ Hemorrhagic cerebrovascular accident
□ other (Specify)

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

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:		

Biocon Biologics
Transforming Healthcare. Transforming Lives.

TARGETED FOLLOW UP FORM- VENOUS THROMBOEMBOLISM (VTE)
BBL Case No.:

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

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

Product Generic (TRADE) Name:

1. Adverse Event Description

Patient's clinical signs and symptoms

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

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

2. Medical History and Concurrent Conditions

Provide details:

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

Genetic risk factors:

TARGETED FOLLOW UP FORM- VENOUS THROMBOEMBOLISM (VTE)
BBL Case No.:

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

Acquired risk factors:

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

If yes to any of the above, provide details

Provide Well's score, if calculated:

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

Diagnostic Test	Results at baseline or prior to use of product (Include date and value/details)	Test results after use of product (Include date 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		

TARGETED FOLLOW UP FORM- VENOUS THROMBOEMBOLISM (VTE)
BBL Case No.:

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		
MethylenetetralHydrofolate 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		

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

Not applicable