EUROPEAN UNION RISK MANAGEMENT PLAN

WEZENLA® (ABP 654, ustekinumab)

Marketing Authorization Holder:	Amgen Technology (Ireland) Unlimited Company Pottery Road, Dun Laoghaire Co. Dublin A96 F2A8 Ireland
Version:	2.0
Date:	17 June 2025
Supersedes:	Version 1.2, dated 09 April 2025

Risk Management Plan (RMP) version to be assessed as part of this application

RMP version number:	2.0
Data lock point of this RMP:	08 March 2022
Date of final sign-off:	17 June 2025
Rationale for submitting an updated RMP:	Added the following to align with the reference medicinal product STELARA® EU RMP: • indication of pediatric Crohn's disease • missing information of 'Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease.'

Summary of significant changes in this RMP

Part/Module/Annex	Major Change(s)	Version Number and Date
Part I: Product(s) Overview	Added the indication and dosage for pediatric Crohn's disease	Version 2.0, 17 June 2025
Part II: Safety Specification		
SVII.2: New Safety Concerns and Reclassification With a Submission of an Updated RMP SVII.3: Details of Important Identified Risks, Important Potential Risks, and Missing Information SVIII: Summary of the Safety Concerns	Added the missing information of 'Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease.'	Version 2.0, 17 June 2025
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	Updated the routine risk minimization activities for the missing information of 'Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease.'	Version 2.0, 17 June 2025
Part VI: Summary of the Risk Management Plan	Updated per changes listed above.	Version 2.0, 17 June 2025
Part VII: Annexes		
Annex 8: Summary of Changes to the Risk Management Plan Over Time	Summary of changes to the risk management plan over time added.	Version 2.0, 17 June 2025

Other RMP versions under evaluation:	
RMP version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP:	
Version number:	1.2
Approved with procedure:	EMEA/H/C/006132/II/0003
Date of approval (opinion date):	14 April 2025
Qualified Person for Pharmacovigilance (QPPV) Name:	Raphaël Van Eemeren, MSc Pharm and MSc Ind Pharm
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization holder's QPPV. The electronic signature is available on file.

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List of Abbreviations

Term/Abbreviation	Explanation
AIDS	acquired immune deficiency syndrome
ATC	Anatomical Therapeutic Chemical
BCG	Bacillus Calmette and Guérin
DMARD	Disease-modifying anti-rheumatic drug
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
HIV	human immunodeficiency virus
IBD	inflammatory bowel disease
ICH	International Council for Harmonisation
IgG1κ	immunoglobulin G1κ
IL	interleukin
INN	International Nonproprietary Name
IV	intravenous(ly)
MTX	methotrexate
OR	odds ratio
PL	package leaflet
PsA	psoriatic arthritis
PSUR	Periodic Safety Update Report
PUVA	psoralen and ultraviolet A
PY	person-years
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
RP	reference product
RPLS	reversible posterior leukoencephalopathy syndrome
SC	subcutaneous(ly)
SmPC	summary of product characteristics
TB	tuberculosis
TNF	tumor necrosis factor
US	United States
VTE	venous thromboembolism

Note to Reviewers: ABP 654 was developed as a biosimilar to STELARA® (ustekinumab). STELARA (ustekinumab) that is approved in, and sourced from, the United States (US) is referred to as "ustekinumab (US)." STELARA (ustekinumab) that is approved in, and sourced from, the European Union (EU) is referred to as "ustekinumab (EU)." The comparator reference medicinal product STELARA is referred to as ustekinumab reference product (RP) in instances where it is used in comparison with ABP 654. In all other contexts in this document, it is referred to as STELARA. The biosimilar to STELARA is referred to as ABP 654 in the Amgen-sponsored studies to be consistent with the marketing application. In all other contexts in this document, it is referred to as WEZENLA.

PART I. PRODUCT(S) OVERVIEW

Table 1. Product(s) Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Ustekinumab
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	Immunosuppressants, interleukin inhibitors, ATC code: L04AC05
Marketing authorization holder	Amgen Technology (Ireland) Unlimited Company
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	WEZENLA
Marketing authorization procedure	Centralized
Brief description of the product	
Chemical class	WEZENLA is a fully human immunoglobulin G1κ (IgG1κ) monoclonal antibody.
Summary of mode of action	Ustekinumab, the active ingredient in WEZENLA, binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-23 and IL-12. Ustekinumab inhibits the bioactivity of human IL-23 and IL-12 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. By binding the shared p40 subunit of IL-23 and IL-12, ustekinumab may exert its clinical effects in plaque psoriasis, psoriatic arthritis (PsA), and Crohn's disease through interruption of the T helper 1 and T helper 17 cytokine pathways, which are central to the pathology of these diseases.
Important information about its composition	Ustekinumab is a fully human IgG1κ monoclonal antibody to IL-23/12 produced in a Chinese hamster ovary cell line using recombinant DNA technology.
Hyperlink to the Product Information (PI)	The proposed PI is provided in Module 1.3.1.

Table 1. Product(s) Overview

Indication(s) in the EEA	
Current	Plaque psoriasis WEZENLA is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A). Pediatric plaque psoriasis WEZENLA 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) WEZENLA, 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 WEZENLA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.
Proposed	Plaque psoriasis WEZENLA is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A). Pediatric plaque psoriasis WEZENLA 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) WEZENLA, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Adult Crohn's disease WEZENLA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist. Pediatric Crohn's disease WEZENLA is indicated for the treatment of moderately to severely active Crohn's disease in pediatric patients weighing at least 40 kg, who have had an inadequate response to, or were intolerant to either conventional or biologic therapy.

Table 1. Product(s) Overview

Dosage in the EEA	
Current	Plaque psoriasis The recommended posology of WEZENLA is an initial dose of 45 mg administered subcutaneously (SC), followed by a 45-mg dose 4 weeks later, then every 12 weeks thereafter. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment. *Patients with body weight > 100 kg* For patients with a body weight > 100 kg, the initial dose is 90 mg administered SC, followed by a 90-mg dose 4 weeks later, and then every 12 weeks thereafter. In these patients, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy. PsA The recommended posology of WEZENLA is an initial dose of 45 mg administered SC, followed by a 45-mg dose 4 weeks later, and then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment. Pediatric plaque psoriasis (6 years and older) The pre-filled pen has not been studied in the pediatric population and is not recommended for use in pediatric patients. The recommended dose of WEZENLA based on body weight is presented in the summary of product characteristics (SmPC) Section 4.2 (Posology and method of administration). WEZENLA should be administered SC 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 WEZENLA treatment is to be initiated with a single intravenous (IV) dose based on body weight, followed by SC doses. The infusion solution for the IV dose is to be composed of the number of vials of WEZENLA 130 mg as specified in SmPC Section 4.2 (Posology and method of administration). The first SC dose should be given at week 8 following the IV dose. For the posology of the subsequent SC dosing regimen, see Section 4.2 of the WEZENLA solution for injection (vial) and solution for injection in pre-filled syringe SmPC or pre-filled pen SmPC.

Table 1. Product(s) Overview

Dosage in the EEA	
Proposed	Plaque psoriasis The recommended posology of WEZENLA is an initial dose of 45 mg administered SC, followed by a 45-mg dose 4 weeks later, and then every 12 weeks thereafter. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment. *Patients with body weight > 100 kg* For patients with a body weight > 100 kg, the initial dose is 90 mg administered SC, followed by a 90-mg dose 4 weeks later, and then every 12 weeks thereafter. In these patients, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy. PsA The recommended posology of WEZENLA is an initial dose of 45 mg administered SC, followed by a 45-mg dose 4 weeks later, and then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment. Pediatric plaque psoriasis (6 years and older) The pre-filled pen has not been studied in the pediatric population and is not recommended for use in pediatric patients. The recommended dose of WEZENLA based on body weight is presented in the summary of product characteristics (SmPC) Section 4.2 (Posology and method of administration). WEZENLA should be administered SC 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. Adult Crohn's disease WEZENLA treatment is to be initiated with a single intravenous (IV) dose based on body weight, followed by SC doses. The infusion solution for the IV dose is to be composed of the number of vials of WEZENLA 130 mg as specified in SmPC Section 4.2 (Posology and method of administration). The first SC dose should be given at week 8 following the IV dose. For the posology of the subsequent SC dosing regimen, see Section 4.2 of the WEZENLA solution for injection (vial) and solution for injection in pre-filled syringe SmPC or pre-filled pen SmPC.

Table 1. Product(s) Overview

Dosage in the EEA

Proposed (continued)

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

WEZENLA 130 mg concentrate for solution for infusion

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

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

[a] Approximately 6 mg/kg

WEZENLA 45 mg solution for injection/ WEZENLA 45 mg solution for injection in pre-filled syringe/ WEZENLA 90 mg solution for injection in pre-filled syringe

The first SC dose should be given at Week 8 following the IV dose.

For the posology of the subsequent SC dosing regimen, see section 4.2 of the WEZENLA solution for injection (vial) and solution for injection in pre-filled syringe SmPC.

Pharmaceutical form(s) and strength(s)

Current

For SC use

The solution is clear to opalescent, colorless to light yellow. The pH of the solution is 6.0.

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.

Solution for injection in pre-filled pen (for adult use): 45 mg/0.5 mL and 90 mg/1 mL.

For IV use

The solution is clear to opalescent, colorless to light yellow.

Concentrate for solution for infusion: 130 mg/26 mL (5 mg/mL).

Proposed

Not applicable.

Is/will the product be subject to additional monitoring in the European Union (EU)?

Yes

PART II. SAFETY SPECIFICATION

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

As per the Guideline on Good Pharmacovigilance Practices Module V - Risk management systems (EMA/838713/2011 Rev 2), Module SI may be omitted from the EU RMP for new applications for similar biological products.

Part II: Module SII - Nonclinical Part of the Safety Specification

ABP 654 was developed as a biosimilar to STELARA (ustekinumab RP). Analytical studies and in vitro pharmacology studies have been conducted to support biosimilarity. Comparability of ABP 654 to STELARA, the reference medicinal product, has been established through physicochemical and biological characterization studies, as recommended in the 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues' (EMEA/CHMP/BMWP/42832/2005 Rev1).

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Important nonclinical safety findings from ABP 654 studies		
Toxicity • Key issues identified from acute or repeat-dose toxicity studies	ABP 654 was not evaluated in single- or repeat-dose in vivo toxicology studies given the lack of toxicological effects observed in the original STELARA toxicology studies and given no residual uncertainty in comparative analytical similarity assessment (inclusive of comprehensive in vitro analytical and functional evaluation). Exclusion of toxicology studies when no uncertainties remain about the safety of ABP 654 is aligned with regulatory guidance for biosimilar development (European Medicines Agency [EMA] 'Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues' [EMA/CHMP/BMWP/403543/2010, 2012]).	ABP 654 is a medicinal product which is biosimilar to STELARA. STELARA has been in clinical use as a marketed medicinal product for over 10 years.
• Reproductive/ developmental toxicity	In line with the EU guidance on biosimilar products (EMA 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: nonclinical and clinical issues' [EMEA/CHMP/BMWP/42832/2005 Rev1, 2014]), reproductive and developmental toxicity studies were not performed for ABP 654.	In line with the reference medicinal product, STELARA, results of reproductive/developmental toxicity studies suggest that administration of ustekinumab is unlikely to adversely affect male or female fertility or fetal development (STELARA EU RMP).
• Genotoxicity	Genotoxicity studies were not performed as they are not applicable for biotechnology-derived pharmaceuticals (EMEA/CHMP/BMWP/42832/2005 Rev1, 2014; International Council for Harmonisation [ICH] S6[R1], Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals, 2011).	Not applicable.

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Important nonclinical safety findings from ABP 654 studies (continued)		
Carcinogenicity	Carcinogenicity studies were not conducted for ABP 654 in alignment with regulatory guidance for biosimilar development (EMEA/CHMP/BMWP/42832/2005 Rev1, 2014).	In line with the reference medicinal product, STELARA, 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 included as an important potential risk (Table 11).
Safety pharmacology • Cardiovascular system (including potential effect on the QT interval) • Nervous system • Other	ABP 654 was not evaluated in safety pharmacology studies given the lack of adverse effects observed in the original STELARA evaluations.	ABP 654 is a medicinal product which is biosimilar to STELARA. STELARA has been in clinical use as a marketed medicinal product for over 10 years.

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Important nonclinical safety findings from STELARA studies		
Toxicity • Key issues identified from acute or repeat-dose toxicity studies	For STELARA, no single-dose toxicity studies were conducted. Repeat-dose toxicity studies in the cynomolgus monkey showed that STELARA was generally well tolerated. Dose levels in animal studies were up to 45 mg/kg twice weekly and approximately 45-fold higher than the highest equivalent dose intended to be administered to psoriasis patients and resulted in peak serum concentrations in monkeys that were more than 100-fold higher than observed in humans (STELARA SmPC; EMA European Public Assessment Report [EPAR], 2009). In the last week of the 26-week chronic toxicity study, 1 monkey in the 45 mg/kg group developed bacterial enteritis and a possible contribution of STELARA to this infection could not be excluded (EMA EPAR, 2009). Published rodent studies suggesting infection risk from inhibition of T helper 1 or T helper 17 cells indicated that IL-23 and IL-12 may contribute to protective immune responses to viral, bacterial, intracellular protozoa, and fungal pathogens (Torti and Feldman, 2007; Bowman et al, 2006).	Adequate margins of exposure over the human clinical exposure were demonstrated (EMA EPAR, 2009). In line with the reference medicinal product, STELARA, serious infections (including mycobacterial and salmonella infections) is included as an important potential risk (Table 10).
• Reproductive/ developmental toxicity	In embryofetal development and postnatal development studies in cynomolgus monkeys at doses up to 45 mg/kg once (IV) or twice (SC) weekly, there was no indication of maternal toxicity, embryotoxicity, teratogenicity, or impact on development of offspring up to 6 months of age. No adverse effects on male fertility indices were observed in monkeys, nor adverse effects on female fertility indices using an analogous antibody to IL-12/23p40 in mice (STELARA SmPC; EMA EPAR, 2009).	In line with the reference medicinal product, STELARA, results of reproductive/developmental toxicity studies suggest that administration of ustekinumab is unlikely to adversely affect male or female fertility or fetal development (STELARA EU RMP).
• Genotoxicity	Genotoxicity tests were not conducted for STELARA (EMA EPAR, 2009).	Not applicable.

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Important nonclinical safety findings from STELARA studies (continued)		
Toxicity (continued) • Carcinogenicity	Carcinogenicity studies were not conducted for STELARA because of the lack of appropriate models for an antibody with limited cross-reactivity to rodent IL-23 or IL-12 (STELARA SmPC; ICH S6[R1], Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals, 2011; EMA EPAR, 2009).	In line with the reference medicinal product, STELARA, 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 included as an important potential risk (Table 11).
Safety pharmacology • Cardiovascular system (including potential effect on the QT interval) • Nervous system • Other	No adverse effects of STELARA were observed in safety pharmacology evaluations following single and repeated dosing in cynomolgus monkeys via IV or SC routes of administration at doses up to 45 mg/kg (EMA EPAR, 2009).	No additional safety concerns were identified from the STELARA nonclinical data.

Part II: Module SIII - Clinical Trial Exposure

Table 3. Total Subject Exposure to ABP 654 or Ustekinumab RP in Clinical Trials by Indication and Duration Safety Analysis Set

Indication	ABP 654		Ustekinumab RP	
	Cumulative Exposure < 6 months n (subj-yrs)	Cumulative Exposure ≥ 6 months n (subj-yrs)	Cumulative Exposure < 6 months n (subj-yrs)	Cumulative Exposure ≥ 6 months n (subj-yrs)
Study 20190230: PK Similarity Study in Healthy Subjects	78 (18.03)	-	159 (36.59)	-
Study 20190232 (FA): Comparative Clinical Study in Subjects with Moderate to Severe Plaque Psoriasis	122 (54.65)	275 (271.93)	6 (1.02)	276 (215.49)
Study 20200359: PK comparability in Healthy Subjects ABP654 delivered via PFS or pre-filled pen	156 (36.30)	-	-	-
Total	356 (108.98)	275 (271.93)	165 (37.61)	276 (215.49)

FA =final analysis; n = number of subjects exposed to ABP 654 or Ustekinumab RP; PFS = pre-filled syringe; PK = pharmacokinetic; RP = reference product; subj-yrs = total subject-years of follow-up.

Safety Analysis Set includes subjects who received at least 1 dose of investigational product.

Note: Data is from the 1) PK similarity study 20190230 (completed on 16JUN2021 with the planned study duration of 112 days), 2) the comparative clinical study 20190232 (completed on 3JUN2022 with the planned study duration of 364 days), and 3) the PK comparability via PFS or pre-filled pen study (completed on 08MAR2022 with the planned study duration of 112 days).

For PK similarity study 20190230 and study 20200359, duration of exposure is calculated as (minimum of (last dose date + 12 weeks, end of study date) - first dose date +1)/365.25. Ustekinumab RP includes both EU sourced and US sourced Ustekinumab RP.

Note: for below description, Period 1 refers to the period before re-randomization. Period 2 refers to the period after re-randomization.

For comparative clinical study 20190232, for subjects who were re-randomized at Week 28 and treated with different IP post Week 28, duration of exposure in Period 1 is calculated as (minimum of (first dose date in Period 2 -1, last dose in Period 1+12 weeks) – first dose date in Period 1 +1)/365.25, and is summarized under the treatment column defined by the actual treatment received before re-randomization; duration of exposure in Period 2 is calculated as (minimum of (cut-off, end of study date, last dose date in Period 2+12 weeks) – first dose date in Period 2 +1)/365.25, and is summarized under the treatment column defined by the actual treatment received after re-randomization. For subjects who were not treated with IP in Period 2, dose intensified subjects, and re-randomized subjects with same IP during the entire study, duration of exposure is calculated as (minimum of (cut-off, end of study date, last dose date + 12 weeks) – first dose date +1)/365.25, and is summarized under the treatment column defined by the actual treatment received during the study.

Source Dataset: ADSL, Program: t-cum-subj-exp.sas, Output: t03-cum-subj-exp.rtf

Table 4. Total Subject Exposure to ABP 654 or Ustekinumab RP in Clinical Trials by Age Group and Gender
Safety Analysis Set

Indication	ABP 654		Ustekinumab RP	
	< 65 years n (subj-yrs)	≥ 65 years n (subj-yrs)	< 65 years n (subj-yrs)	≥ 65 years n (subj-yrs)
Male				
Study 20190230: PK Similarity Study in Healthy Subjects	39 (9.05)	0 (0)	78 (17.95)	0 (0)
Study 20190232 (FA): Comparative Clinical Study in Subjects with Moderate to Severe Plaque Psoriasis	233 (191.59)	18 (15.72)	179 (139.48)	12 (9.33)
Study 20200359: PK comparability in Healthy Subjects ABP654 delivered via PFS or pre-filled pen	75 (17.45)	0 (0)	-	-
Total	347 (218.10)	18 (15.72)	257 (157.42)	12 (9.33)
Female				
Study 20190230: PK Similarity Study in Healthy Subjects	39 (8.98)	0 (0)	81 (18.64)	0 (0)
Study 20190232 (FA): Comparative Clinical Study in Subjects with Moderate to Severe Plaque Psoriasis	133 (107.96)	13 (11.30)	82 (60.38)	9 (7.33)
Study 20200359: PK comparability in Healthy Subjects ABP654 delivered via PFS or pre-filled pen	81 (18.85)	0 (0)	-	-
Total	253 (135.80)	13 (11.30)	163 (79.02)	9 (7.33)

FA =final analysis; n = number of subjects exposed to ABP 654 or Ustekinumab RP; PFS = pre-filled syringe; PK = pharmacokinetic; RP = reference product; subj-yrs = total subject-years of follow-up.

Safety Analysis Set includes subjects who received at least 1 dose of investigational product.

Note: Data is from the 1) PK similarity study 20190230 (completed on 16JUN2021 with the planned study duration of 112 days), 2) the comparative clinical study 20190232 (completed on 3JUN2022 with the planned study duration of 364 days), and 3) the PK comparability via PFS or pre-filled pen study (completed on 08MAR2022 with the planned study duration of 112 days).

For PK similarity study 20190230 and study 20200359, duration of exposure is calculated as (minimum of (last dose date + 12 weeks, end of study date) - first dose date +1)/365.25. Ustekinumab RP includes both EU sourced and US sourced Ustekinumab RP.

Note: for below description, Period 1 refers to the period before re-randomization. Period 2 refers to the period after re-randomization.

For comparative clinical study 20190232, for subjects who were re-randomized at Week 28 and treated with different IP post Week 28, duration of exposure in Period 1 is calculated as (minimum of (first dose date in Period 2 -1, last dose in Period 1+12 weeks) – first dose date in Period 1 +1)/365.25, and is summarized under the treatment column defined by the actual treatment received before re-randomization; duration of exposure in Period 2 is calculated as (minimum of (cut-off, end of study date, last dose date in Period 2+12 weeks) – first dose date in Period 2 +1)/365.25, and is summarized under the treatment column defined by the actual treatment received after re-randomization. For subjects who were not treated with IP in Period 2, dose intensified subjects, and re-randomized subjects with same IP during the entire study, duration of exposure is calculated as (minimum of (cut-off, end of study date, last dose date + 12 weeks) – first dose date +1)/365.25, and is summarized under the treatment column defined by the actual treatment received during the study.

Source Dataset: ADSL, Program: t-cum-subj-exp-age-sex.sas, Output: t04-cum-subj-exp-age-sex.rtf

Table 5. Exposure to ABP 654 or Ustekinumab RP in Clinical Trials by Dose Level and Indication
Safety Analysis Set

Indication	Exposure to ABP 654 in Days			Exposure to Ustekinumab RP in Days			Exposure to ABP 654 in Subject-years			Exposure to Ustekinumab RP in Subject-years		
	90 mg Single Dose [a] n (mean)	45 mg Q4W Q8W Q12W [b] n (mean)	90 mg Q4W Q8W Q12W [c] n (mean)	90 mg Single Dose [a] n (mean)	45 mg Q4W Q8W Q12W [b] n (mean)	90 mg Q4W Q8W Q12W [c] n (mean)	90 mg Single Dose [a] n (total)	45 mg Q4W Q8W Q12W [b] n (total)	90 mg Q4W Q8W Q12W [c] n (total)	90 mg Single Dose [a] n (total)	45 mg Q4W Q8W Q12W [b] n (total)	90 mg Q4W Q8W Q12W [c] n (total)
Study 20190230: PK Similarity Study in Healthy Subjects	78 (84.4)	-	-	159 (84.1)	-	-	78 (18.03)	-	-	159 (36.59)	-	-
Study 20190232 (FA): Comparative Clinical Study in Subjects with Moderate to Severe Plaque Psoriasis	-	265 (301.7)	132 (297.9)	-	190 (285.6)	92 (269.8)	-	265 (218.92)	132 (107.66)	-	190 (148.57)	92 (67.95)
Study 20200359: PK comparability in Healthy Subjects ABP654 delivered via PFS or pre-filled pen	156 (85.0)	-	-	-	-	-	156 (36.30)	-	-	-	-	-

Footnotes, including abbreviations, are defined on the last page of the table.

Table 5. Exposure to ABP 654 or Ustekinumab RP in Clinical Trials by Dose Level and Indication
Safety Analysis Set

Indication	Exposure to ABP 654 in Days			Exposure to Ustekinumab RP in Days			Exposure to ABP 654 in Subject-years			Exposure to Ustekinumab RP in Subject-years		
	90 mg Single Dose [a] n (mean)	45 mg Q4W Q8W Q12W [b] n (mean)	90 mg Q4W Q8W Q12W [c] n (mean)	90 mg Single Dose [a] n (mean)	45 mg Q4W Q8W Q12W [b] n (mean)	90 mg Q4W Q8W Q12W [c] n (mean)	90 mg Single Dose [a] n (total)	45 mg Q4W Q8W Q12W [b] n (total)	90 mg Q4W Q8W Q12W [c] n (total)	90 mg Single Dose [a] n (total)	45 mg Q4W Q8W Q12W [b] n (total)	90 mg Q4W Q8W Q12W [c] n (total)
Total	234 (84.8)	265 (301.7)	132 (297.9)	159 (84.1)	190 (285.6)	92 (269.8)	234 (54.34)	265 (218.92)	132 (107.66)	159 (36.59)	190 (148.57)	92 (67.95)

FA =final analysis; n = number of subjects exposed to ABP 654 or Ustekinumab RP; PFS = pre-filled syringe; PK = pharmacokinetic; RP = reference product; subj-yrs = total subject-years of follow-up.

Safety Analysis Set includes subjects who received at least 1 dose of investigational product.

Note: Data is from the 1) PK similarity study 20190230 (completed on 16JUN2021 with the planned study duration of 112 days), 2) the comparative clinical study 20190232 (completed on 3JUN2022 with the planned study duration of 364 days), and 3) the PK comparability via PFS or pre-filled pen study (completed on 08MAR2022 with the planned study duration of 112 days).

For PK similarity study 20190230 and study 20200359, duration of exposure is calculated as (minimum of (last dose date + 12 weeks, end of study date) - first dose date +1)/365.25. Ustekinumab RP includes both EU sourced and US sourced Ustekinumab RP.

Note: for below description, Period 1 refers to the period before re-randomization. Period 2 refers to the period after re-randomization.

For comparative clinical study 20190232, for subjects who were re-randomized at Week 28 and treated with different IP post Week 28, duration of exposure in Period 1 is calculated as (minimum of (first dose date in Period 2 -1, last dose in Period 1+12 weeks) –first dose date in Period 1 +1)/365.25, and is summarized under the treatment column defined by the actual treatment received before re-randomization; duration of exposure in Period 2 is calculated as (minimum of (cut-off, end of study date, last dose date in Period 2+12 weeks) – first dose date in Period 2 +1)/365.25, and is summarized under the treatment column defined by the actual treatment received after re-randomization. For subjects who were not treated with IP in Period 2, dose intensified subjects, and re-randomized subjects with same IP during the entire study, duration of exposure is calculated as (minimum of (cut-off, end of study date, last dose date + 12 weeks) – first dose date +1)/365.25, and is summarized under the treatment column defined by the actual treatment received during the study.

[a] 90 mg Single Dose includes both PFS and pre-filled pen injections.

[b] 45 mg includes initial dose (Q4W), maintenance dose (Q12W) and dose intensification (Q8W) for subjects with baseline weight <=100kg.

[c] 90 mg includes initial dose (Q4W), maintenance dose (Q12W) and dose intensification (Q8W) for subjects with baseline weight >100kg.

Source Dataset: ADSL, ADEX, Program: t-exp-by-dose.sas, Output: t05-exp-by-dose.rtf

Table 6. Total Subject Exposure to ABP 654 or Ustekinumab RP in Clinical Trials by Product and Race/Ethnic Group
Safety Analysis Set

Indication	ABP 654 n (subj-yrs)	Ustekinumab RP n (subj-yrs)
Study 20190230: PK Similarity Study in Healthy Subjects		
Ethnic Group		
Hispanic or Latino	14 (3.26)	32 (7.45)
Not Hispanic or Latino	64 (14.77)	127 (29.14)
Total	78 (18.03)	159 (36.59)
Race		
American Indian or Alaska Native	1 (0.23)	2 (0.47)
Asian	15 (3.49)	36 (8.30)
Black or African American	14 (3.14)	28 (6.39)
Multiple	2 (0.47)	4 (0.93)
Native Hawaiian or Other Pacific Islander	0 (0)	1 (0.23)
White	46 (10.70)	88 (20.27)
Total	78 (18.03)	159 (36.59)
Study 20190232 (FA): Comparative Clinical Study in Subjects with Moderate to Severe Plaque Psoriasis		
Ethnic Group		
Hispanic or Latino	40 (33.77)	28 (20.96)
Not Hispanic or Latino	355 (291.37)	252 (194.02)
Not Reported	1 (1.00)	0 (0)
Unknown	1 (0.44)	2 (1.53)
Total	397 (326.58)	282 (216.51)

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 6. Total Subject Exposure to ABP 654 or Ustekinumab RP in Clinical Trials by Product and Race/Ethnic Group
Safety Analysis Set

Indication	ABP 654 n (subj-yrs)	Ustekinumab RP n (subj-yrs)
Race		
American Indian or Alaska Native	1 (1.00)	2 (2.00)
Asian	30 (24.41)	25 (19.32)
Black or African American	5 (4.23)	2 (1.53)
Multiple	1 (1.00)	0 (0)
Native Hawaiian or Other Pacific Islander	1 (0.46)	1 (0.54)
White	351 (289.06)	247 (189.56)
Other	7 (5.41)	5 (3.56)
Not Reported	1 (1.00)	0 (0)
Total	397 (326.58)	282 (216.51)
Study 20200359: PK comparability in Healthy Subjects ABP654 delivered via PFS or pre-filled pen		
Ethnic Group		
Hispanic or Latino	66 (15.36)	-
Not Hispanic or Latino	89 (20.71)	-
Not Reported	1 (0.23)	-
Total	156 (36.30)	-
Race		
American Indian or Alaska Native	1 (0.23)	-
Asian	9 (2.09)	-
Black or African American	49 (11.40)	-
Multiple	4 (0.93)	-
White	93 (21.64)	-
Total	156 (36.30)	-

Footnotes, including abbreviations, are defined on the last page of the table.

Table 6. Total Subject Exposure to ABP 654 or Ustekinumab RP in Clinical Trials by Product and Race/Ethnic Group
Safety Analysis Set

Indication	ABP 654 n (subj-yrs)	Ustekinumab RP n (subj-yrs)
Total		
Ethnic Group		
Hispanic or Latino	120 (52.38)	60 (28.40)
Not Hispanic or Latino	508 (326.85)	379 (223.16)
Not Reported	2 (1.23)	0 (0)
Unknown	1 (0.44)	2 (1.53)
Total	631 (380.91)	441 (253.10)
Race		
American Indian or Alaska Native	3 (1.46)	4 (2.46)
Asian	54 (30.00)	61 (27.62)
Black or African American	68 (18.77)	30 (7.92)
Multiple	7 (2.40)	4 (0.93)
Native Hawaiian or Other Pacific Islander	1 (0.46)	2 (0.77)
White	490 (321.40)	335 (209.83)
Other	7 (5.41)	5 (3.56)
Not Reported	1 (1.00)	0 (0)
Total	631 (380.91)	441 (253.10)

FA =final analysis; n = number of subjects exposed to ABP 654 or Ustekinumab RP; PFS = pre-filled syringe; PK = pharmacokinetic; RP = reference product; subj-yrs = total subject-years of follow-up.

Safety Analysis Set includes subjects who received at least 1 dose of investigational product.

Note: Data is from the 1) PK similarity study 20190230 (completed on 16JUN2021 with the planned study duration of 112 days), 2) the comparative clinical study 20190232 (completed on 3JUN2022 with the planned study duration of 364 days), and 3) the PK comparability via PFS or pre-filled pen study (completed on 08MAR2022 with the planned study duration of 112 days).

For PK similarity study 20190230 and study 20200359, duration of exposure is calculated as (minimum of (last dose date + 12 weeks, end of study date) - first dose date +1)/365.25. Ustekinumab RP includes both EU sourced and US sourced Ustekinumab RP.

Note: for below description, Period 1 refers to the period before re-randomization. Period 2 refers to the period after re-randomization.

For comparative clinical study 20190232, for subjects who were re-randomized at Week 28 and treated with different IP post Week 28, duration of exposure in Period 1 is calculated as (minimum of (first dose date in Period 2 -1, last dose in Period 1+12 weeks) – first dose date in Period 1 +1)/365.25, and is summarized under the treatment column defined by the actual treatment received before re-randomization; duration of exposure in Period 2 is calculated as (minimum of (cut-off, end of study date, last dose date in Period 2+12 weeks) – first dose date in Period 2 +1)/365.25, and is summarized under the treatment column defined by the actual treatment received after re-randomization. For subjects who were not treated with IP in Period 2, dose intensified subjects, and re-randomized subjects with same IP during the entire study, duration of exposure is calculated as (minimum of (cut-off, end of study date, last dose date + 12 weeks) – first dose date +1)/365.25, and is summarized under the treatment column defined by the actual treatment received during the study.

Source Dataset: ADSL, Program: t-cum-subj-exp-ethnic-race.sas, Output: t06-cum-subj-exp-ethnic-race.rtf

Part II: Module SIV - Populations Not Studied in Clinical Trials

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

ABP 654 was developed as a biosimilar to STELARA. Table 7 reflects the important exclusion criteria for ABP 654 as well as for STELARA.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Hypersensitivity to the investigational product or to any of the excipients	This is a contraindication for ABP 654 and the reference medicinal product, STELARA.	No	In line with the reference medicinal product STELARA, WEZENLA is contraindicated in patients with a known hypersensitivity to the active substance or to any of the excipients. It is not possible to predict which patients may develop a hypersensitivity reaction to WEZENLA. Additional information regarding hypersensitivity reactions that may occur during treatment with WEZENLA is provided in SmPC Section 4.4, Special warnings and precautions for use.
Active infection (including infections treated with systemic anti-infectives or requiring hospitalization within a specified time) or history of recurrent or chronic infectious disease	Treatment with immunomodulatory agents may increase the risk of infection or worsen an existing infection.	No	In line with the reference medicinal product STELARA, serious infections (including mycobacterial and salmonella infections) is included as an important potential risk (Table 10) and WEZENLA is contraindicated in patients with clinically important active infection such as active tuberculosis (TB). Information regarding the potential to increase the risk of infections and reactivate latent infections is included in SmPC Section 4.4, Special warnings and precautions for use, in line with the reference medicinal product, STELARA.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Pregnancy or breastfeeding, or planning to become pregnant	Per ICH guidance, pregnant women are generally excluded from clinical studies. 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.	No	Data from a moderate number of prospectively collected pregnancies following exposure to ustekinumab with known outcomes, including more than 450 pregnancies exposed during the first trimester, do not indicate an increased risk of major congenital malformations in the newborn (STELARA SmPC). In line with the reference medicinal product STELARA, SmPC Section 4.6, Fertility, pregnancy and lactation advises as a precautionary measure, it is preferable to avoid the use of WEZENLA during pregnancy, and advises the use of effective methods of contraception during treatment and for at least 15 weeks after treatment. Because of the potential for adverse reactions in nursing infants from ustekinumab, a decision on whether to discontinue breastfeeding during treatment and up to 15 weeks after treatment, or to discontinue therapy with WEZENLA, must be made taking into account the benefit of breastfeeding to the child and the benefit of WEZENLA therapy to the woman.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Known malignancy within the previous 5 years (except treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma)	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 of malignancy associated with administration of ustekinumab is supported by published literature that reported dysregulated tumor growth in mouse models with decreased IL-12 activity (Airoldi et al, 2005; Brunda et al, 1993). Therefore, patients with malignancy were excluded.	No	In line with the reference medicinal product STELARA, use in patients with concurrent malignancy or a history of malignancy is no longer considered missing information. As immunosuppressants like ustekinumab have the potential to increase the risk of malignancy, guidance for the use of WEZENLA in patients with a history of malignancy and in patients who continue treatment after developing malignancy while receiving WEZENLA is provided in SmPC Section 4.4, Special warnings and precautions for use.
Received live viral or live bacterial vaccination within 2 weeks prior to randomization	Administration of live vaccines during immunomodulatory therapy may increase the risk of active infection following vaccination.	No	In line with the reference medicinal product STELARA, SmPC Section 4.4, Special warnings and precautions for use, recommends that before live viral or live bacterial vaccination, treatment with WEZENLA should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Uncontrolled, clinically significant systemic disease such as uncontrolled diabetes mellitus, cardiovascular disease, renal disease, liver disease, or hypertension Active neurological disease such as multiple sclerosis, Guillain-Barre syndrome, optic neuritis, transverse myelitis, or history of neurologic symptoms suggestive of central nervous system demyelinating disease Moderate to severe heart failure	This is a precautionary position applied to clinical study subjects when a drug has not been widely used in humans.	No	In line with the reference medicinal product STELARA, the impracticalities of identifying adequate numbers of patients with progressive concomitant disease in each of these categories precludes the further study of WEZENLA in these patient populations. Given the severity of disease in subjects with severe, progressive, or uncontrolled disease, the risk-benefit balance of the use of WEZENLA should be carefully evaluated on a case-by-case basis.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. However, this is a biosimilar medicinal product and there is extensive experience of clinical and postmarketing use of the reference medicinal product STELARA.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 8. Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Three pregnancies were reported in the ABP 654 clinical development program. Data from a moderate number of prospectively collected pregnancies following exposure to STELARA with known outcomes, including more than 450 pregnancies exposed during the first trimester, do not indicate an increased risk of major congenital malformations in the newborn (STELARA SmPC).
Breastfeeding women	Breastfeeding women were not included in the ABP 654 and reference medicinal product STELARA clinical development programs.
Patients with relevant comorbidities	
Patients with hepatic impairment	Not included in the ABP 654 and reference medicinal product STELARA clinical development programs.
Patients with renal impairment	Not included in the ABP 654 and reference medicinal product STELARA clinical development programs.
Patients with cardiovascular impairment	Not included in the ABP 654 and reference medicinal product STELARA clinical development programs.
Immunocompromised patients	Not included in the ABP 654 and reference medicinal product STELARA clinical development programs.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the ABP 654 and reference medicinal product STELARA clinical development programs.
Population with relevant different ethnic origin	ABP 654 and STELARA have been studied in subject populations of a variety of racial backgrounds and ethnicity in clinical studies (Table 6).
Subpopulations carrying relevant genetic polymorphisms	Not included in the ABP 654 and reference medicinal product STELARA clinical development programs.
Other Pediatric patients	Pediatric patients were not included in the ABP 654 clinical development program. The reference medicinal product STELARA was studied in children 6 years of age and older.

Part II: Module SV - Postauthorization Experience

SV.1 Postauthorization Exposure

Postmarketing data are currently not available.

SV.1.1 Method Used to Calculate Exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

Postauthorization Use From Business Partners

Not applicable.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

No evidence to suggest a potential for drug abuse or misuse has been observed. The reference medicinal product, STELARA, is not associated with any abuse potential.

Part II: Module SVII - Identified and Potential Risks

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

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

The risks not considered important for inclusion in the list of safety concerns in the RMP are not described here due to the lack of available data for the reference medicinal product. Please refer to the full safety profile in the SmPC for WEZENLA and the EU RMP for the reference medicinal product, STELARA.

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

WEZENLA is a biosimilar product; therefore, the list of safety concerns considered important is aligned with that of the reference medicinal product, STELARA.

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

Table 9. New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification
New Safety Concerns		
Missing Information		
Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease	Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease is new missing information	This risk has been added to align with the reference medicinal product STELARA EU RMP.

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

The important identified risks, important potential risks, and missing information presented for WEZENLA are presented as per the EU RMP of STELARA with the following exception: the missing information 'long-term safety in adult patients with moderately to severely active ulcerative colitis' was not included as WEZENLA is not indicated for the treatment of ulcerative colitis. No new safety concerns were identified in the WEZENLA clinical program.

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

Table 10. Important Potential Risk: Serious Infections (Including Mycobacterial and Salmonella Infections)

Potential mechanisms	Studies performed in mice suggest that IL-23 may contribute to immunity to *Klebsiella pneumoniae* (Happel et al, 2005), *Mycobacterium tuberculosis* (Khader et al, 2005), *Cryptococcus neoformans* (Kleinschek et al, 2006), and *Candida albicans* (Acosta-Rodriguez et al, 2007), and that IL-12 may contribute to protective immune responses to intracellular protozoa, bacteria, and fungal pathogens (Trinchieri, 2003). Humans who are genetically deficient for IL-12/23p40 or IL-12Rβl and who are presumed to be deficient in both IL-23 and IL-12 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 Bacillus Calmette and Guérin (BCG), and recurring *Salmonella sp.* (Novelli and Casanova, 2004; Fieschi and Casanova, 2003). Filipe-Santos et al (2006) reviewed inborn errors of IL-12/23 and reported that these patients, when vaccinated with BCG, developed BCG disease. They also found that these patients were more susceptible to salmonella infections.
Evidence source(s) and strength of evidence	This important potential risk is included per the reference medicinal product STELARA. Evidence sources: STELARA SmPC, and ABP 654 clinical study of plaque psoriasis.
Characterization of the risk	
Frequency	**ABP 654 study:** In Study 20190232, the subject incidence of adverse events of serious infections[a] was 2 of 397 subjects (0.5%; 95% CI: 0.1, 1.8) while receiving ABP 654 treatment and 5 of 282 subjects (1.8%; 95% CI: 0.6, 4.1) while receiving ustekinumab RP treatment. There were no events of mycobacterial or salmonella infections. **STELARA studies:** In clinical studies and a postmarketing observational study in patients with psoriasis, serious bacterial, fungal, and viral infections have been observed in patients receiving STELARA. Opportunistic infections including reactivation of TB, 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 STELARA. In the placebo-controlled studies of patients with psoriasis, PsA, Crohn's disease, and ulcerative colitis, the rates of infection or serious infection were similar between STELARA-treated patients and those treated with placebo.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 10. Important Potential Risk: Serious Infections (Including Mycobacterial and Salmonella Infections)

Characterization of the risk (continued)	
Frequency (continued)	In the placebo-controlled period of these clinical studies, the rate of infection was 1.36 per patient-year of follow-up in STELARA-treated patients and 1.34 in placebo-treated patients (STELARA SmPC). Serious infections occurred at the rate of 0.03 per patient-year of follow-up in STELARA-treated patients (30 serious infections in 930 patient-years of follow-up) and 0.03 in placebo-treated patients (15 serious infections in 434 patient-years of follow-up). In the controlled and non-controlled periods of psoriasis, PsA, Crohn's disease, and ulcerative colitis clinical studies, representing 11 581 patient-years of exposure in 6709 patients, the median follow-up was 1.0 year; 1.1 years for psoriatic disease studies, 0.6 years for Crohn's disease studies, and 1.0 year for ulcerative colitis studies. The rate of infection was 0.91 per patient-year of follow-up in STELARA-treated patients, and the rate of serious infections was 0.02 per patient-year of follow-up in STELARA-treated patients (199 serious infections in 11 581 patient-years of follow-up) and serious infections reported included pneumonia, anal abscess, cellulitis, diverticulitis, gastroenteritis, and viral infections. In clinical studies, patients with latent TB who were concurrently treated with isoniazid did not develop TB. In clinical studies and in the postmarketing setting, cellulitis was reported as an uncommon adverse reaction (STELARA SmPC).
Severity	In Study 20190232, the adverse events of serious infections[a] reported in subjects while receiving ABP 654 treatment were severe (grade 3); no events had a fatal outcome. In subjects receiving ustekinumab reference product treatment, adverse events of serious infections[a] ranged in severity from moderate (grade 2) to fatal (grade 5).
Reversibility	Serious infections may resolve with administration of appropriate treatment. However, serious infections are potentially life threatening or fatal.
Long-term outcomes	Long-term outcome data are not available for WEZENLA, but are expected to be comparable to STELARA.
Impact on quality of life	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 WEZENLA or will have to choose a medication other than WEZENLA. Patients with active infections will have to choose an alternative medication and discontinue use of WEZENLA 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 WEZENLA. This important potential risk needs to be carefully weighed against the benefit conferred by use of WEZENLA.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 10. Important Potential Risk: Serious Infections (Including Mycobacterial and Salmonella Infections)

Risk factors and risk groups	Risk factors for the development of serious infections include diabetes and other comorbidities, as well as the concomitant use of steroids, anti-TNFs, other immunosuppressants, or other biologics. The most common risk factors for the development of TB include conditions impairing the development of effective cell-mediated immunity to the infection (ie, advanced age, human immunodeficiency virus [HIV] infection), alcohol abuse, malignancy, corticosteroids or other immunosuppression, connective tissue disease, renal failure, diabetes, and pregnancy. A risk factor for the development of TB is exposure to TB, and patients who were born or lived in countries considered by the World Health Organization to have a high TB burden (incidence: $>$ 300 TB cases/100 000 population/year) or have travelled to these locations may be at higher risk. Exposure in the health care setting or in high-density institutions (ie, prisons) may also put patients at higher risk of development of TB. The possibility of latent TB must be considered, especially in patients who have immigrated from or travelled to countries with a high prevalence of TB or had close contact with a person with active TB. In patients who are severely ill or immunocompromised, tuberculin tests may yield false negative results. A retrospective/prospective review performed in Australia, found that significant risks for non-HIV-associated pulmonary *Mycobacterium avium*/*Mycobacterium intracellulare* complex disease included male sex (odds ratio [OR] = 2.1; 95% CI: 1.0, 4.5) and age $>$ 50 years (OR = 26.5; 95% CI: 10.9, 67.3; O'Brien et al, 2000). Similarly, in a US study (Cassidy et al, 2009) including 933 patients with 1 or more non-TB mycobacterial 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 non-TB mycobacterial pulmonary disease (Andréjak et al, 2013). Prolonged occupational exposure to soil was an important risk factor for *Mycobacterium avium*/*Mycobacterium intracellulare* complex infection in a US study (Reed et al, 2006). Factors that could increase risk of salmonella infection include activities that result in close contact with salmonella (eg, international travel, owning a pet bird or reptile) and health issues that weaken resistance to infection (eg, use of antacids; recent antibiotic use; inflammatory bowel disease [IBD]; or impaired immunity from HIV/acquired immune deficiency syndrome [AIDS], sickle cell disease, malaria, anti-rejection drugs taken after organ transplants, and corticosteroids) (Mayo Clinic, 2022).

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 10. Important Potential Risk: Serious Infections (Including Mycobacterial and Salmonella Infections)

Preventability	WEZENLA is contraindicated in patients with a clinically important, active infection (eg, active TB). To prevent serious infections, it is recommended that live vaccines not be given concurrently with WEZENLA. For infants exposed to ustekinumab in utero, administration of live vaccines is not recommended for 12 months following birth or until ustekinumab infant serum levels are undetectable. Caution should be exercised when considering the use of WEZENLA in patients with a chronic infection or a history of recurrent infection. 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 WEZENLA should not be administered until the infection resolves. WEZENLA must not be given to patients with active TB. WEZENLA should not be given to patients with latent TB unless treatment for latent TB is initiated prior to administering WEZENLA, including those patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving WEZENLA should be monitored closely for signs and symptoms of active TB during and after treatment. Specific recommendations about the prevention of non-TB mycobacterial infections are not available. 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 risk of serious infections (including mycobacterial and salmonella infections) has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labeling.
Public health impact	The public health impact is not expected to be greater than the reference medicinal product STELARA.

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AIDS = acquired immune deficiency syndrome; BCG = Bacillus Calmette and Guérin; HIV = human immunodeficiency virus; IBD = inflammatory bowel disease; OR = odds ratio; PsA = psoriatic arthritis; SmPC = summary of product characteristics; TB = tuberculosis; US = United States

[a] For identification of events suggestive of serious infections (including mycobacterial and salmonella infections), the following search strategy was utilized: Infections and infestations System Organ Class (SOC) limited to adverse events Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher, or terms reported as serious. Data are from the final analysis of the study with data cut-off date of 03 June 2022.

Table 11. Important Potential Risk: Malignancy

Potential mechanisms	Scientific literature suggests that IL-12 can contribute to tumor immunosurveillance (Colombo and Trinchieri, 2002) and exogenous IL-12 can promote tumor-directed cytotoxic T-cell responses in tumor vaccine strategies. In contrast, IL-23 has been reported to promote tumor growth in animal models. The preponderance of evidence from the published literature (knockout models where IL-23 is ablated) suggests that a risk for malignancy may actually be reduced in the setting of IL-23 inhibition. However, conflicting data from a limited number of studies in mouse models and from photocarcinogenicity experiments point to an increased risk of malignancy in IL-23p19-deficient mice exposed to ultraviolet B radiation. Studies in mice genetically deficient in IL-12, or mice treated with high doses of an anti-mouse IL-12/23p40 antibody, suggest that IL-12 contributes to immunity against certain mouse models of neoplasia (Rao et al, 1997). Cardenes et al (2010) described a 25-year-old patient with IL-12Rβl deficiency who developed esophageal carcinoma. However, the contribution of endogenous human IL-23 or IL-12 to tumor immunosurveillance remains unclear.
Evidence source(s) and strength of evidence	This important potential risk is included per the reference medicinal product STELARA. Evidence sources: STELARA SmPC, and ABP 654 clinical study of plaque psoriasis.
Characterization of the risk	
Frequency	**ABP 654 study:** In Study 20190232, the subject incidence of adverse events of malignancy[a] was 3 of 397 subjects (0.8%; 95% CI: 0.2, 2.2) while receiving ABP 654 treatment and 2 of 282 subjects (0.7%; 95% CI: 0.1, 2.5) while receiving ustekinumab reference product (RP) treatment. **STELARA studies:** Some patients who received STELARA in clinical studies and in a postmarketing observational study in patients with psoriasis developed cutaneous and non-cutaneous malignancies. In the placebo-controlled period of the psoriasis, PsA, Crohn's disease, and ulcerative colitis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.11 per 100 patient-years of follow-up for STELARA-treated patients (1 patient in 929 patient-years of follow-up) compared with 0.23 for placebo-treated patients (1 patient in 434 patient-years of follow-up). The incidence of non-melanoma skin cancer was 0.43 per 100 patient-years of follow-up for STELARA-treated patients (4 patients in 929 patient-years of follow-up) compared to 0.46 for placebo-treated patients (2 patients in 433 patient-years of follow-up). In the controlled and non-controlled periods of psoriasis, PsA, Crohn's disease, and ulcerative colitis clinical studies, representing 11 561 patient-years of exposure in 6709 patients, the median follow-up was 1.0 year; 1.1 years for psoriatic disease studies, 0.6 years for Crohn's disease studies, and 1.0 year for ulcerative colitis studies (STELARA SmPC).

Footnotes, including abbreviations, are defined on the last page of the table.

Table 11. Important Potential Risk: Malignancy

Characterization of the risk (continued)	
Frequency (continued)	Malignancies excluding non-melanoma skin cancers were reported in 62 patients in 11 561 patient-years of follow-up (incidence of 0.54 per 100 patient-years of follow-up for STELARA-treated patients). The incidence of malignancies reported in STELARA-treated patients was comparable to the incidence expected in the general population (standardized incidence ratio = 0.93 [95% CI: 0.71, 1.20], adjusted for age, gender, and race). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, colorectal, melanoma, and breast cancers. The incidence of non-melanoma skin cancer was 0.49 per 100 patient-years of follow-up for STELARA-treated patients (56 patients in 11 545 patient-years of follow-up). The ratio of patients with basal versus squamous cell skin cancers (3:1) is comparable with the ratio expected in the general population (STELARA SmPC).
Severity	In Study 20190232, the adverse events of malignancy[a] in subjects while receiving ABP 654 treatment were reported as mild (grade 1) or severe (grade 3); no events had a fatal outcome. Where outcome was reported, the events had resolved. In subjects receiving ustekinumab RP treatment, adverse events of malignancy[a] were moderate (grade 2) in severity.
Reversibility	Reversibility would depend on the severity and nature of the malignancy.
Long-term outcomes	Long-term outcome data are not available for WEZENLA, but are expected to be comparable to STELARA.
Impact on quality of life	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 WEZENLA. This important potential risk needs to be carefully weighed against the benefit conferred by use of WEZENLA.
Risk factors and risk groups	Among psoriasis patients, increased risk of solid cancers appears to be related to alcohol drinking and cigarette smoking. In addition, exposure to PUVA and immunosuppressants, including cyclosporin and possibly MTX, has been associated with squamous cell carcinoma in psoriasis patients (Pouplard et al, 2013). General risk factors for malignancy include increasing age, lifestyle factors (such as use of alcohol and tobacco and obesity), family history of cancer, and certain environmental exposures. Risk factors for the development of malignancy can differ by cancer site. However, in general, factors that can increase risk of malignancies in IBD patients include but are not limited to smoking, ongoing inflammation, and carcinogenic effects of immunosuppressive drugs.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 11. Important Potential Risk: Malignancy

Preventability	Predictability and preventability of the development of malignancy is not known. Protection from ultraviolet exposure, either solar or from tanning beds, may decrease the risk of an individual developing a cutaneous malignancy. Caution should be exercised when considering the use of WEZENLA in patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy. All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy, or those with a history of PUVA treatment, should be monitored for the appearance of skin cancer. No testing is available to identify patients at risk for cutaneous malignancy.
Impact on the risk-benefit balance of the product	The risk of malignancy has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labeling.
Public health impact	The public health impact is not expected to be greater than the reference medicinal product STELARA.

IBD = inflammatory bowel disease; IL = interleukin; MTX = methotrexate; PsA = psoriatic arthritis; PUVA = psoralen and ultraviolet A; RP = reference product; SmPC = summary of product characteristics

[a] For identification of events suggestive of malignancy, the following search strategy was utilized: Malignancies Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ; narrow scope). Data are from the final analysis of the study with data cut-off date of 03 June 2022.

Table 12. Important Potential Risk: Cardiovascular Events

Potential mechanisms	Patients with severe psoriasis are more likely to demonstrate cardiovascular risk factors such as obesity, diabetes, and hypertension when compared with those with no or mild psoriasis (Neimann et al, 2006). The greatest risk of myocardial infarction is found in young patients with severe psoriasis (Gelfand et al, 2006). As in psoriasis, patients with PsA are reported to be at increased risk for occlusive vascular diseases, including myocardial infarction and stroke (Li et al, 2012; Husted et al, 2011; Tobin et al, 2010; Gladman et al, 2009). The potential mechanistic link between psoriasis and cardiovascular events, if any, is unclear.
Evidence source(s) and strength of evidence	This important potential risk is included per the reference medicinal product STELARA. Evidence sources: STELARA SmPC, and ABP 654 clinical study of plaque psoriasis.
Characterization of the risk	
Frequency	**ABP 654 study:** In Study 20190232, the subject incidence of cardiovascular events[a] was 3 of 397 subjects (0.8%; 95% CI: 0.2, 2.2) while receiving ABP 654 treatment and 4 of 282 subjects (1.4%; 95% CI: 0.4, 3.6) while receiving ustekinumab reference product (RP) treatment. **STELARA studies:** Cardiovascular events including myocardial infarction and cerebrovascular accident have been observed in patients with psoriasis exposed to STELARA in a postmarketing observational study (STELARA SmPC).
Severity	In Study 20190232, the cardiovascular events[a] in subjects while receiving ABP 654 treatment were reported as mild (grade 1); no events had a fatal outcome. In subjects receiving ustekinumab RP treatment, cardiovascular events[a] were mild (grade 1) or severe (grade 3).
Reversibility	Reversibility would depend on the severity and nature of the cardiovascular event.
Long-term outcomes	Long-term outcome data are not available for WEZENLA, but are expected to be comparable to STELARA.
Impact on quality of life	There is evidence for an increased background risk of cardiovascular disease in patients with psoriasis and IBD, and patients may experience debilitating myocardial infarction, stroke, or death. Patients are not considered at further cardiovascular risk from use of WEZENLA beyond that related to the psoriasis or IBD population risk. Patients with psoriasis and IBD require vigilance in adequate treatment of cardiovascular risk factors including hypertension, hypercholesterolemia, and diabetes. The impact of major adverse cardiovascular events on the individual patient is potentially significant. Major adverse cardiovascular events may result in fatal outcome.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 12. Important Potential Risk: Cardiovascular Events

Risk factors and risk groups	The risk factors in the development of cardiovascular disease are well known and include hypertension, hypercholesterolemia, diabetes, smoking, age, male sex, obesity, and family history. The PsA, psoriasis, and Crohn's disease populations share certain risk factors such as increased cardiovascular risk, increased body weight, and increased body mass index (Bostoen et al, 2014; Dregan et al, 2014; Kristensen et al, 2013; Román and Muñoz, 2011; Augustin et al, 2010).
Preventability	The preventability of cardiovascular disease is based upon the modification of known risk factors. A relationship between cardiovascular events and WEZENLA is not established. The effects of STELARA on hypertension, diabetes, glycemic control, and weight were evaluated in the phase 3 psoriasis and PsA studies and no apparent impact was found.
Impact on the risk-benefit balance of the product	The risk of cardiovascular events has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive.
Public health impact	The public health impact is not expected to be greater than the reference medicinal product STELARA.

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IBD = inflammatory bowel disease; PsA = psoriatic arthritis; RP = reference product; SmPC = summary of product characteristics

[a] For identification of events suggestive of cardiovascular events, the following search strategy was utilized: Cardiac disorders System Organ Class (SOC). Data are from the final analysis of the study with data cut-off date of 03 June 2022.

Table 13. 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 WEZENLA could cause depression is not known.
Evidence source(s) and strength of evidence	This important potential risk is included per the reference medicinal product STELARA. Evidence sources: STELARA SmPC, and ABP 654 clinical study of plaque psoriasis.
Characterization of the risk	
Frequency	**ABP 654 study:** There were no adverse events of serious depression including suicidality[a] reported in Study 20190232. **STELARA studies:** In clinical studies and in the postmarketing setting, depression was reported as an uncommon adverse reaction (STELARA SmPC).
Severity	No adverse events of serious depression including suicidality[a] were reported in Study 20190232. Severity data for ABP 654 are expected to be comparable to STELARA.
Reversibility	Depression may resolve with appropriate treatment.
Long-term outcomes	Long-term outcome data are not available for WEZENLA, but are expected to be comparable to STELARA.
Impact on quality of life	The impact of depression on the individual patient may be very significant, and patients with a history of untreated or inadequately treated depression should be treated for such. There may be psychosocial impact and possibility of death from suicide attempts.
Risk factors and risk groups	Risk factors for depression include older age and associated neurological conditions; uncontrolled, poorly treated psoriasis; recent childbirth; stressful life events; a personal or family history of depression; and selected medical comorbid conditions including psoriatic conditions and IBD. Suicide rates are twice as high in families of suicide victims (Fancher and Kravitz, 2007).
Preventability	There is no known means of preventing depression.
Impact on the risk-benefit balance of the product	The risk of serious depression, including suicidality, has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive.
Public health impact	The public health impact is not expected to be greater than the reference medicinal product STELARA.

IBD = inflammatory bowel disease; SmPC = summary of product characteristics

[a] For identification of events suggestive of serious depression including suicidality, the following search strategy was utilized: Depression and suicide/self-injury Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ; broad scope) limited to adverse events Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher, or terms reported as serious. Data are from the final analysis of the study with data cut-off date of 03 June 2022.

Table 14. Important Potential Risk: Venous Thromboembolism

Potential mechanisms	Currently, there is no known mechanism by which WEZENLA could induce or exacerbate venous thromboembolism. The available literature shows that IL-23 and IL-12 are not implicated in the process of venous thrombosis. However, patients with IBD are at higher risk of venous thrombosis. Venous thromboembolism in patients with IBD is a multifactorial event that involves both hereditary (factor V Leiden mutation, G20210A mutation of the prothrombin gene, and homozygous C677T mutation in the methylenetetrahydrofolate reductase gene) and acquired factors (dehydration, indwelling catheters, prolonged immobilization, hyperhomocysteinemia, surgical interventions, active disease with a high inflammatory burden, hospitalization, colonic localization, recent surgery, oral contraceptive use, etc). The pathogenesis of thrombosis in IBD is complex and not fully known. In patients with IBD, several mechanisms triggered by active inflammation may contribute to a higher prothrombotic state. These mechanisms include: • Increased plasma levels of recognized risk factors for thrombosis (eg, TNFα, IL-6, and IL-8 levels, several of which are also considered to be acute-phase reactant) and decreased levels of natural anticoagulants • Reduced fibrinolytic activity • Endothelial abnormalities that are mainly represented by the downregulation of the anticoagulant thrombomodulin and endothelial protein C receptor, which in turn affects the conversion of protein C into its activated form • Abnormalities of platelets, such as thrombocytosis and increased activation and aggregation (Papa et al, 2014). WEZENLA inhibits IL-23/12 and the inhibition of IL-23 is associated with reduced plasma levels of the pro-inflammatory cytokines (TNFα, IL-6, and IL-8) that have been implicated in thrombogenesis. Therefore, currently there is no evidence to suggest biologic plausibility for the inhibition of IL-23/12 contributing to the development of thrombosis.
Evidence source(s) and strength of evidence	This important potential risk is included per the reference medicinal product STELARA. Evidence sources: STELARA SmPC, and ABP 654 clinical study of plaque psoriasis.
Characterization of the risk	
Frequency	**ABP 654 study:** There were no adverse events of venous thromboembolism[a] reported in Study 20190232. **STELARA studies:** There were no venous thromboembolism events reported in the STELARA SmPC.
Severity	No adverse events of venous thromboembolism[a] were reported in Study 20190232. Severity data for ABP 654 are expected to be comparable to STELARA.

Footnotes, including abbreviations, are defined on the last page of the table.

Table 14. Important Potential Risk: Venous Thromboembolism

Characterization of the risk (continued)	
Reversibility	Venous thromboembolism may resolve with appropriate treatment. However, events of venous thromboembolism are potentially fatal.
Long-term outcomes	Long-term outcome data are not available for WEZENLA, but are expected to be comparable to STELARA.
Impact on quality of life	The impact of venous thromboembolism 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 venous thromboembolism events including events of deep vein thrombosis, pulmonary embolism, or splanchnic vein thrombosis with or without fatal outcome. The occurrence of venous thromboembolism imparts a greater risk of in-hospital mortality among hospitalized IBD patients that is greater than the greater mortality risk imparted by venous thromboembolism in the non-IBD population (Nguyen et al, 2014). Patients with IBD require vigilance in adequate treatment of venous thromboembolism risk factors.
Risk factors and risk groups	Patients suffering from IBD, namely Crohn's disease and ulcerative colitis, are more prone to thromboembolic complications compared with the general population (Zezos et al, 2014). A study of IBD patients conducted in the United Kingdom reported that there was increased risk of venous thromboembolism during disease flares and chronic activity, (Grainge et al, 2010). In a Danish population study that included children and adults, and the highest risk of venous thromboembolism was in the 0 to 20 years age group with a hazard ratio of 6.6 (95% CI: 3.3, 13.2) compared with 1.6 (95% CI: 1.5, 1.8) for the > 60 years age group (Kappelman et al, 2011). Risk has also been reported to be greater for males (incidence rate of 1.34 per 1000 person-years [PY]) than for females (incidence rate of 0.73 per 1000 PY). Smoking and the need for steroid treatment have also been shown to be risk factors for venous thromboembolism with ORs of 3.46 (95% CI: 1.14, 10.5) and 2.97 (95% CI: 0.99, 8.92), respectively (Vegh et al, 2015).
Preventability	Patients with risk factors for venous thrombosis may require prophylactic anticoagulation. The preventability is also aimed at reducing acquired risk factors through appropriate measures like providing adequate hydration, effective anti-inflammatory treatment, early mobilization after surgery, graduated compression stockings or pneumatic devices, limited and rational use of venous catheters, weight loss, alternative methods of contraception, etc.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 14. Important Potential Risk: Venous Thromboembolism

Impact on the risk-benefit balance of the product	The risk of venous thromboembolism has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive.
Public health impact	The public health impact is not expected to be greater than the reference medicinal product STELARA.

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IBD = inflammatory bowel disease; IL = interleukin; OR = odds ratio; PY = person-years; SmPC = summary of product characteristics; TNF = tumor necrosis factor

[a] For identification of events suggestive of venous thromboembolism, the following search strategy was utilized: Embolic and thrombotic events, venous Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ; narrow scope). Data are from the final analysis of the study with data cut-off date of 03 June 2022.

SVII.3.2 Presentation of the Missing Information

Table 15. Missing Information: Long-term Safety in Pediatric Psoriasis Patients 6 Years and Older

Evidence source	Missing information for WEZENLA is included per the reference medicinal product STELARA. Pediatric patients were not studied in the WEZENLA clinical program as per the Guidelines for Biosimilars (Regulation [EC] No 1901/2006 [Paediatric Regulation] amended by Regulation [EC] No 1902/2008). The safety of STELARA has been studied in two phase 3 studies of pediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks and the second study was in 44 patients from 6 to 11 years of age treated for up to 56 weeks (STELARA SmPC).
Population in need of further characterization	Pediatric patients with psoriasis, 6 years of age and older, with long-term exposure to WEZENLA.

SmPC = summary of product characteristics

Table 16. Missing Information: Long-term Impact on Growth and Development in Pediatric Psoriasis Patients 6 Years and Older

Evidence source	Missing information for WEZENLA is included per the reference medicinal product STELARA. Pediatric patients were not studied in the WEZENLA clinical program as per the Guidelines for Biosimilars (Regulation [EC] No 1901/2006 [Paediatric Regulation] amended by Regulation [EC] No 1902/2008). The safety of STELARA has been studied in two phase 3 studies of pediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks and the second study was in 44 patients from 6 to 11 years of age treated for up to 56 weeks (STELARA SmPC).
Population in need of further characterization	Pediatric patients with psoriasis, 6 years of age and older, with long-term exposure to WEZENLA.

SmPC = summary of product characteristics

Table 17. Missing Information: Long-term Safety in Adult Patients With Moderately to Severely Active Crohn's Disease

Evidence source	Missing information for WEZENLA is included per the reference medicinal product STELARA. Patients with Crohn's disease were not included in the WEZENLA clinical program. A total of 567 patients with Crohn's disease received treatment with STELARA for up to 5 years in an extension study (STELARA SmPC).
Population in need of further characterization	Adults with moderately to severely active Crohn's disease with long-term exposure to WEZENLA.

SmPC = summary of product characteristics

Table 18. Missing Information: Long-term Safety Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease

Evidence source	Missing information for WEZENLA is included per the reference medicinal product STELARA RMP. A relatively small number of pediatric subjects aged 2 to < 18 years and weighing 40 kg and above (40 male and 42 female) were exposed to ustekinumab reference medicinal product in the pediatric Crohn's disease clinical trials (STELARA EU RMP). Patients with Crohn's disease were not included in the WEZENLA clinical program.
Population in need of further characterization	Pediatric patients with moderately to severely active Crohn's disease and weighing 40 kg and above with long-term exposure to WEZENLA.

RP = reference product; RMP = Risk Management Plan

Part II: Module SVIII - Summary of the Safety Concerns

Table 19. Summary of Safety Concerns

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

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are presented in Table 20 and Table 21.

Table 20. Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
Ustekinumab targeted follow-up questionnaire for serious infections and opportunistic infections Ustekinumab targeted follow-up questionnaire for tuberculosis	Serious infections (including mycobacterial and salmonella infections)	To further characterize events of serious infections, opportunistic infections, and tuberculosis reported in patients treated with WEZENLA in the postmarketing environment.
Ustekinumab follow-up questionnaire for malignancies (including lymphoma, second, and secondary malignancies)	Malignancy	To further characterize events of malignancies (including lymphoma, second, and secondary malignancies) reported in patients treated with WEZENLA in the postmarketing environment.
Ustekinumab targeted follow-up questionnaire for cardiovascular events	Cardiovascular events	To further characterize cardiovascular events reported in patients treated with WEZENLA in the postmarketing environment.
Ustekinumab targeted follow-up questionnaire for venous thromboembolism (VTE)	Venous thromboembolism	To further characterize events of venous thromboembolism reported in patients treated with WEZENLA in the postmarketing environment.

Table 21. Other Forms of Routine Pharmacovigilance Activities

Description of Activity	Safety Concern(s)	Objectives	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 postmarketing environment.	Not applicable

III.2 Additional Pharmacovigilance Activities

There are no ongoing or planned additional pharmacovigilance activities.

III.3 Summary Table of Additional Pharmacovigilance Activities

There are no ongoing or planned WEZENLA category 1 to 3 studies.

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

The safety information in the proposed WEZENLA SmPC is aligned to the reference medicinal product STELARA SmPC.

V.1 Routine Risk Minimization Measures

Table 22. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Potential Risks	
Serious infections (including mycobacterial and salmonella infections)	Routine risk communication: • SmPC Sections 4.3, 4.4, 4.5, 4.6, and 4.8 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • 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 WEZENLA; recommendation to monitor patients for signs and symptoms of active TB during and after WEZENLA treatment; guidance for managing patients who develop a serious infection; and recommendations regarding the administration of live vaccines to patients receiving WEZENLA and to infants exposed to WEZENLA in utero, are included in SmPC Section 4.4. • Recommendations regarding the administration of live vaccines to patients receiving WEZENLA and to infants exposed to WEZENLA in utero are included in SmPC Section 4.5. • Recommendation regarding the administration of live vaccines to infants exposed to WEZENLA in utero is included in SmPC Section 4.6. • Guidance for patients who have recently had or are going to have a vaccination; guidance for mothers who received WEZENLA while pregnant and recommendation regarding the administration of live vaccines to infants exposed to WEZENLA in utero; and 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, is included in PL Section 2. • Guidance for patients who develop signs of an infection or have open cuts or sores while using WEZENLA is included in PL Section 4. Other routine risk minimization measures beyond the PI: • Legal status: Restricted medical prescription

Table 22. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Potential Risks (continued)	
Malignancy	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Guidance for monitoring patients for the appearance of skin cancer is included in SmPC Section 4.4. Other routine risk minimization measures beyond the PI: • 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 PI: • Legal status: Restricted medical prescription
Serious depression including suicidality	Routine risk communication: • SmPC Section 4.8 • PL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • None Other routine risk minimization measures beyond the PI: • 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 PI: • Legal status: Restricted medical prescription

Table 22. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Missing Information	
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 PI: • 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 PI: • 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 PI: • Legal status: Restricted medical prescription
Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease	Routine risk communication: • None Routine risk minimization activities recommending specific clinical measures to address the risk: • None Other routine risk minimization measures beyond the PI: • Legal status: Restricted medical prescription

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V.2 Additional Risk Minimization Measures

Routine risk minimization measures as described in Part V.1 are sufficient to manage the safety concerns of WEZENLA.

V.3 Summary of Risk Minimization Measures

Table 23. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
None		
Important Potential Risks		
Serious infections (including mycobacterial and salmonella infections)	Routine risk minimization measures: • SmPC Section 4.3 • SmPC Section 4.4 where guidance regarding TB infection, serious infection, and administration of live vaccines is included • SmPC Sections 4.5 and 4.6 where guidance regarding administration of live vaccines is included • SmPC Section 4.8 • PL Sections 2 and 4 • Legal status: Restricted medical prescription Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaires Additional pharmacovigilance activities: • None
Malignancy	Routine risk minimization measures: • SmPC Section 4.4 where guidance for monitoring patients for the appearance of skin cancer is included • SmPC Section 4.8 • PL Section 2 • Legal status: Restricted medical prescription Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None

Table 23. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks (continued)		
Cardiovascular events	Routine risk minimization measures: • Legal status: Restricted medical prescription Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Serious depression including suicidality	Routine risk minimization measures: • SmPC Section 4.8 • PL Section 4 • Legal status: Restricted medical prescription 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: • Legal status: Restricted medical prescription Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None

Table 23. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing Information		
Long-term safety in pediatric psoriasis patients 6 years and older	Routine risk minimization measures: • Legal status: Restricted medical prescription 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: • Legal status: Restricted medical prescription Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Long-term safety in adult patients with moderately to severely active Crohn's disease	Routine risk minimization measures: • Legal status: Restricted medical prescription Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease	Routine risk minimization measures: • Legal status: Restricted medical prescription 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

A summary of the RMP for WEZENLA is presented below.

Summary of Risk Management Plan for WEZENLA® (ustekinumab)

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

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

This summary of the RMP for WEZENLA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 WEZENLA's RMP.

I. The Medicine and What it is Used for

WEZENLA is indicated for plaque psoriasis, pediatric plaque psoriasis, psoriatic arthritis, adult Crohn's disease and pediatric Crohn's disease (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 WEZENLA's benefits can be found in WEZENLA's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/wezenla.

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

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

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

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

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

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

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

II.A. List of Important Risks and Missing Information

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

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

II.B. Summary of Important Risks

Important potential risk: Serious infections (including mycobacterial and salmonella infections)	
Evidence for linking the risk to the medicine	This important potential risk is included per the reference medicinal product STELARA. Evidence sources: STELARA SmPC, and ABP 654 clinical study of plaque psoriasis.
Risk factors and risk groups	Risk factors for the development of serious infections include diabetes and other comorbidities, as well as the concomitant use of steroids, anti-TNFs, other immunosuppressants, or other biologics. The most common risk factors for the development of tuberculosis (TB) include conditions impairing the development of effective cell-mediated immunity to the infection (ie, advanced age, human immunodeficiency virus [HIV] infection), alcohol abuse, malignancy, corticosteroids or other immunosuppression, connective tissue disease, renal failure, diabetes, and pregnancy. A risk factor for the development of TB is exposure to TB, and patients who were born or lived in countries considered by the World Health Organization to have a high TB burden (incidence: > 300 TB cases/100 000 population/year) or have travelled to these locations may be at higher risk. Exposure in the health care setting or in high-density institutions (ie, prisons) may also put patients at higher risk of development of TB. The possibility of latent TB must be considered, especially in patients who have immigrated from or travelled to countries with a high prevalence of TB or had close contact with a person with active TB. In patients who are severely ill or immunocompromised, tuberculin tests may yield false negative results. A retrospective/prospective review performed in Australia, found that significant risks for non-HIV-associated pulmonary *Mycobacterium avium*/*Mycobacterium intracellulare* complex disease included male sex (odds ratio [OR] = 2.1; 95% CI: 1.0, 4.5) and age > 50 years (OR = 26.5; 95% CI: 10.9, 67.3). Similarly, in a United States (US) study including 933 patients with 1 or more non-TB mycobacterial 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 non-TB mycobacterial pulmonary disease. Prolonged occupational exposure to soil was an important risk factor for *Mycobacterium avium*/*Mycobacterium intracellulare* complex infection in a US study). Factors that could increase risk of salmonella infection include activities that result in close contact with salmonella (eg, international travel, owning a pet bird or reptile) and health issues that weaken resistance to infection (eg, use of antacids; recent antibiotic use; inflammatory bowel disease [IBD]; or impaired immunity from HIV/acquired immune deficiency syndrome [AIDS], sickle cell disease, malaria, anti-rejection drugs taken after organ transplants, and corticosteroids).

Important potential risk: Serious infections (including mycobacterial and salmonella infections) (continued)	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.3 • SmPC Section 4.4 where guidance regarding TB infection, serious infection, and administration of live vaccines is included • SmPC Sections 4.5 and 4.6 where guidance regarding administration of live vaccines is included • SmPC Section 4.8 • PL Sections 2 and 4 • Legal status: Restricted medical prescription Additional risk minimization measures: • None

Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	This important potential risk is included per the reference medicinal product STELARA. Evidence sources: STELARA SmPC, and ABP 654 clinical study of plaque psoriasis.
Risk factors and risk groups	Among psoriasis patients, increased risk of solid cancers appears to be related to alcohol drinking and cigarette smoking. In addition, exposure to psoralen and ultraviolet A and immunosuppressants, including cyclosporin and possibly methotrexate, has been associated with squamous cell carcinoma in psoriasis patients. General risk factors for malignancy include increasing age, lifestyle factors (such as use of alcohol and tobacco and obesity), family history of cancer, and certain environmental exposures. Risk factors for the development of malignancy can differ by cancer site. However, in general, factors that can increase risk of malignancies in IBD patients include but are not limited to smoking, ongoing inflammation, and carcinogenic effects of immunosuppressive drugs.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 where guidance for monitoring patients for the appearance of skin cancer is included • SmPC Section 4.8 • PL Section 2 • Legal status: Restricted medical prescription Additional risk minimization measures: • None

Important potential risk: Cardiovascular events	
Evidence for linking the risk to the medicine	This important potential risk is included per the reference medicinal product STELARA. Evidence sources: STELARA SmPC, and ABP 654 clinical study of plaque psoriasis.
Risk factors and risk groups	The risk factors in the development of cardiovascular disease are well known and include hypertension, hypercholesterolemia, diabetes, smoking, age, male sex, obesity, and family history. The psoriatic arthritis, psoriasis, and Crohn's disease populations share certain risk factors such as increased cardiovascular risk, increased body weight, and increased body mass index.
Risk minimization measures	Routine risk minimization measures: • Legal status: Restricted medical prescription Additional risk minimization measures: • None

Important potential risk: Serious depression including suicidality	
Evidence for linking the risk to the medicine	This important potential risk is included per the reference medicinal product STELARA. Evidence sources: STELARA SmPC, and ABP 654 clinical study of plaque psoriasis.
Risk factors and risk groups	Risk factors for depression include older age and associated neurological conditions; uncontrolled, poorly treated psoriasis; recent childbirth; stressful life events; a personal or family history of depression; and selected medical comorbid conditions including psoriatic conditions and IBD. Suicide rates are twice as high in families of suicide victims.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8 • PL Section 4 • Legal status: Restricted medical prescription Additional risk minimization measures: • None

Important potential risk: Venous thromboembolism	
Evidence for linking the risk to the medicine	This important potential risk is included per the reference medicinal product STELARA. Evidence sources: STELARA SmPC, and ABP 654 clinical study of plaque psoriasis.
Risk factors and risk groups	Patients suffering from IBD, namely Crohn's disease and ulcerative colitis, are more prone to thromboembolic complications compared with the general population. A study of IBD patients conducted in the United Kingdom reported that there was increased risk of venous thromboembolism during disease flares and chronic activity. In a Danish population study that included children and adults, and the highest risk of venous thromboembolism was in the 0 to 20 years age group with a hazard ratio of 6.6 (95% CI: 3.3, 13.2) compared with 1.6 (95% CI: 1.5, 1.8) for the > 60 years age group. Risk has also been reported to be greater for males (incidence rate of 1.34 per 1000 person-years [PY]) than for females (incidence rate of 0.73 per 1000 PY). Smoking and the need for steroid treatment have also been shown to be risk factors for venous thromboembolism with ORs of 3.46 (95% CI: 1.14, 10.5) and 2.97 (95% CI: 0.99, 8.92), respectively.
Risk minimization measures	Routine risk minimization measures: • Legal status: Restricted medical prescription Additional risk minimization measures: • None

Missing information: Long-term safety in pediatric psoriasis patients 6 years and older	
Risk minimization measures	Routine risk minimization measures: • Legal status: Restricted medical prescription Additional risk minimization measures: • None

Missing information: Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	
Risk minimization measures	Routine risk minimization measures: • Legal status: Restricted medical prescription Additional risk minimization measures: • None

Missing information: Long-term safety in adult patients with moderately to severely active Crohn's disease	
Risk minimization measures	Routine risk minimization measures: • Legal status: Restricted medical prescription Additional risk minimization measures: • None

Missing information: Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease	
Risk minimization measures	Routine risk minimization measures: • Legal status: Restricted medical prescription Additional risk minimization measures: • None

II.C. Postauthorization Development Plan

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

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

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

There are no studies required for WEZENLA.

PART VII: ANNEXES

Table of Contents

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Follow-up forms

Follow-up Form Title	Date of Follow-up Version
Ustekinumab targeted follow-up questionnaire for serious infections and opportunistic infections	31 October 2023
Ustekinumab targeted follow-up questionnaire for tuberculosis	31 October 2023
Ustekinumab follow-up questionnaire for malignancies (including lymphoma, second, and secondary malignancies)	31 October 2023
Ustekinumab targeted follow-up questionnaire for cardiovascular events	31 October 2023
Ustekinumab targeted follow-up questionnaire for venous thromboembolism (VTE)	31 October 2023

AMGEN

Ustekinumab Targeted Follow-up Questionnaire for Serious Infections and Opportunistic Infections

Date of this report (dd/mm/yyyy):

AER #:

1. PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate dates as dd/mm/yyyy)

Patient Identifier (if using DOB: dd/mm/yyyy) | Patient initials: | Gender: ☐ Male ☐ Female | Weight: ____ lb ____ kg | Date of event onset (dd/mm/yyyy) | Event reported term | Safety Database No.

Age at time of event: _____ Height: _____

Patient ethnicity: _____ ☐ Unknown

Co-suspect medications (include start and stop date): _____

2. USTEKINUMAB ADMINISTRATION (Please indicate dates as dd/mm/yyyy)

Indication for use: ☐ Plaque Psoriasis ☐ Psoriatic Arthritis ☐ Crohn's Disease ☐ Ulcerative Colitis ☐ Other _____

Ustekinumab Dose _____ Frequency _____ Route _____

Batch # _____ Exp Date _____ ☐ Unknown Batch #

Ustekinumab Exposure: First administered (start date) _____

Last dose before event (date): _____ Doses given prior to event: _____

Doses were skipped: ☐ No ☐ Yes (specify dates/reason) _____ ☐ Unknown

Ustekinumab discontinued: ☐ No ☐ Yes (specify dates/reason) _____ ☐ Unknown

3. ADVERSE EVENT DETAILS, SIGNS AND SYMPTOMS (please provide dates and details)

☐ Type of infection (eg, pneumonia, endocarditis, etc.) and location, if relevant (eg, subcutaneious abscess of the forearm or TB of the CNS): _____

☐ There were unusual features of the patient's presentation (details): _____

☐ Infection was present prior to starting the product (details): _____

Symptoms: Date of first symptoms: _____ ☐ Other symptoms (specify): _____

☐ Fever _____
☐ Cough _____
☐ Swelling (location) _____
☐ Pain (location) _____
☐ Rash (location) _____
☐ Shortness of breath _____
☐ Diarrhea _____
☐ Discharge (location) _____
☐ Description _____
☐ Chills _____
☐ Night sweats _____
☐ Prolonged fatigue _____

☐ Organ system affected:
- ☐ Cardiac
- ☐ Ear/nose
- ☐ Throat
- ☐ Gastrointestinal
- ☐ Respiratory
- ☐ Kidney/genito-urinary
- ☐ Musculoskeletal (including joints)
- ☐ Nervous (cerebrospinal fluid)
- ☐ Skin (details/location): _____
- ☐ Systemic (bacteremia and/or sepsis)
- ☐ Other _____

4. EVALUATIONS AND LABORATORIES AT TIME OF EVENT(S) (please attach copies of reports, if available)

Diagnostic	Results/Units	Normal Reference Range	Date	Report Attached Y	N
Vital signs on initial assessment:					
Blood pressure					
Respiratory rate					
Body temperature					
Heart rate					
O_2 saturation					
Hemoglobin					
Hematocrit					
WBC with differential					
Lymphocytes					
Monocytes					
Neutrophils					
Eosinophils					
Reticulocytes					
Platelet count					
CRP					

Diagnostic	Results/Units	Normal Reference Range	Date	Report Attached Y	N
Fibrinogen					
ESR					
Other inflammatory marker					
D-Dimer					
BUN/Creatine					
LDH					
Haptoglobin					
ALT					
AST					
Alkaline phophatase					
Direct/Total bilirubin					
Arterial blood gases					
Culture (specify)					
TB Test: Skin/Blood					
Other labs (specify)					

5. REPORTS/RELEVANT FINDINGS (indicate diagnostic, provide dates, results, and indicate attachments if available. Indicate dates as dd/mm/yyyy)

Diagnostic Report	Result Details	Date performed

CONTINUED ON NEXT PAGE

6. MEDICAL HISTORY AND CONCURRENT CONDITIONS (Please provide details)

Please specify any post operative complications, chronic disease or infection, etc.

- ☐ Immunocompromised (underlying diagnoses, immunosuppressive therapy, etc., specify) _____
- ☐ Details of vaccination history _____
- ☐ Chronic lung disease _____
- ☐ Hepatitis _____
- ☐ Chronic kidney disease _____
- ☐ Liver disease _____
- ☐ Congenital infections/malformations _____
- ☐ Osteomyelitis _____
- ☐ HIV _____
- ☐ Diabetes mellitus _____
- ☐ Cancer (specify) _____
- ☐ Recent wounds/infections _____
- ☐ Known exposure to TNF inhibitors _____
- ☐ Chemotherapy _____
- ☐ Malnutrition/Failure to thrive _____
- ☐ Prior exposure to TB _____
- ☐ Prior exposure to hepatitis B/C _____
- ☐ Exposure to infectious agents:
  - ☐ Personal contact _____ ☐ Body fluids _____
  - ☐ Share personal items (razor, needles, etc)
  - ☐ Potentially contaminated food/liquid
  - ☐ Hospital acquired _____
  - ☐ Other _____
- ☐ Steroid exposure _____
- ☐ Insect/tick bite _____
- ☐ Drug or IV drug abuse: Type _____
  - ☐ Amount _____
  - ☐ Frequency _____
- ☐ Alcohol/tobacco use: Type _____
  - ☐ Amount _____
  - ☐ Frequency _____
- ☐ Indwelling catheters _____
- ☐ Recent skin injury _____
- ☐ Recent travel (specify) _____
- ☐ Exposure to animals/zoonotic diseases (exposure to infected animal) _____
- ☐ Unprotected sex _____
- ☐ Immobility _____
- ☐ Indwelling catheters _____
- ☐ Nursing home resident _____
- ☐ Occupational exposure _____
- ☐ Ostomy _____
- ☐ Post influenza _____
- ☐ Surgery < 30 days _____
- ☐ Other relevant history/risk factors for acquiring infection: _____

7. CONCOMITANT MEDICATIONS (Please specify including start and stop date. Include dietary supplements and OTC medications)

Drug name	Indication for use	Dose/Frequency/Route	Start date(dd/mm/yyyy)	Stop date (dd/mm/yyyy)

8. TREATMENT AND RESPONSE (Please specify patient treatment regimen, response, and outcome of event. Provide dates, attach reports)

Diagnosis: _____ Date of diagnosis: _____ Date(s) of hospitalization _____

Treatment Regimen (Please specify treatment including start and stop date. Include OTC medications):

Treatment (ie, medication, etc.)	Details (ie, Dose/Frequency/Route)	Response to Treatment	Start date(dd/mmyyyy)	Stop date (dd/mm/yyyy)

Did the event resolve? ☐ Yes (provide date) _____ ☐ No (specify details) _____

Was ustekinumab re-administered after the event? ☐ Yes (specify details) _____ ☐ No

Did the event recur or worsen? ☐ Yes (specify details) _____ ☐ No

Any unusual features of the clinical course? ☐ Yes (specify details) _____ ☐ No

9. COMMENTS (please provide additional relevant details as necessary)

_____

_____

_____

_____

_____

Return completed form to Amgen via email: svc-ags-in-us@amgen.com
or fax: 1-888-814-8653

REPORTER Name:

Address:

City:

Country:

Email:

Phone/Fax: (include country code)

Signature: _____ Date _____

Title/Role/Organization _____

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AMGEN

Ustekinumab Targeted Follow-up Questionnaire for Tuberculosis

Date of this report (dd/mm/yyyy): | AER #: |

1. PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate dates as dd/mm/yyyy)

Patient Identifier (if using DOB: dd/mm/yyyy) | Patient initials: | Gender: ☐ Male ☐ Female | Weight: ____ lb ____ kg | Date of event onset (dd/mm/yyyy) | Event reported term | Safety Database No.

Age at time of event: _____ Height: _____

Patient ethnicity: _____ ☐ Unknown

Co-suspect medications (include start and stop date): _____

2. USTEKINUMAB ADMINISTRATION (Please indicate dates as dd/mm/yyyy)

Indication for use: ☐ Plaque Psoriasis ☐ Psoriatic Arthritis ☐ Crohn's Disease ☐ Ulcerative Colitis ☐ Other _____

Ustekinumab Dose _____ Frequency _____ Route _____

Batch # _____ Exp Date _____ ☐ Unknown Batch #

Ustekinumab Exposure: First administered (start date) _____

Last dose before event (date): _____ Doses given prior to event: _____

Doses were skipped: ☐ No ☐ Yes (specify dates/reason) _____ ☐ Unknown

Ustekinumab discontinued: ☐ No ☐ Yes (specify dates/reason) _____ ☐ Unknown

3. EVALUATIONS AND LABORATORIES AT TIME OF EVENT(S) (List additional details below and attach report[s] if available)

PURIFIED PROTEIN DERIVATIVE (PPD) TESTING was performed: ☐ Yes ☐ No

If yes, indicate skin test used: ☐ Intradermal ☐ Multipuncture

Number of units administered: _____

PPD result: _____ mm of induration (0 if no duration) Date _____

2nd PPD result: _____ mm of induration (0 if no duration) Date _____

☐ False negative test (eg, time of injection to time of evaluation too long/short, evaluator of induration, etc.)

Explain reasons: _____

If results were positive, did patient have active TB? ☐ Yes ☐ No

Type of TB: ☐ Pulmonary ☐ Extrapulmonary; location: _____ ☐ Multi-drug resistant TB ☐ Disseminated; location: _____

CHEST X-RAY (CXR) was performed: ☐ Yes ☐ No

Provide CXR results just prior to ustekinumab dosing or any time in past: _____

Date of prior CXR (dd/mm/yyyy): _____

Provide CXR results at diagnosis of TB: _____

Date of CXR at diagnosis (dd/mm/yyyy): _____

Provide repeat CXR results: _____

Date of repeat CXR (dd/mm/yyyy): _____

Diagnostic	Results/Units	Reference Range	Date	Report Attached Y	N
AFB Smear: Sputum					
Other (specify)					
Other (specify)					
Culture: Sputum					
Other (specify)					
Other (specify)					
PCR MTb					
Quantiferon TB Gold					
Other (specify)					
Hemoglobin					
Hematocrit					
RBC					
WBC with differential					
Lymphocytes					
Neutrophils					
Eosinophils					

Diagnostic	Results/Units	Reference Range	Date	Report Attached Y	N
Reticulocytes					
Platelet count					
Vital signs/initial assessment:					
Blood pressure					
Respiratory rate					
Body temperature					
Heart rate					
O_2 saturation					
CRP					
Fibrinogen					
D-Dimer					
BUN/Creatine					
LDH					
Haptoglobin					
ALT/AST					
Other (specify)					

Other consult report (specify): _____

Hospital admission/discharge report: _____

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AMGEN

Ustekinumab Targeted Follow-up Questionnaire for Tuberculosis

Date of this report (dd/mm/yyyy):

AER #:

4. RELEVANT MEDICAL / OCCUPATIONAL HISTORY (Check all that apply and provide details)

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

5. CONCOMITANT MEDICATIONS (Please specify including start and stop date. Include dietary supplements and OTC medications, attach reports)

Drug name	Indication for use	Dose/Frequency/Route	Start date(dd/mm/yyyy)	Stop date (dd/mm/yyyy)

6. TREATMENT, RESPONSE and OUTCOME (Please provide dates and indicate attachments if available)

Date of first TB symptoms (dd/mm/yyyy) _____ Date of TB diagnosis: _____

Time elapsed from onset of TB symptoms until treatment was instituted (hours, days): _____

Was patient given prophylactic therapy? ☐ Yes (provide details in table below) ☐ No

Drug name (include dose/route)	Start date (dd/mm/yyyy)	Stop date (dd/mm/yyyy)

Treatment Regimen:

Medication _____ _____

Total Daily Dose/Route _____ _____

Start Date _____ Stop Date _____

Medication _____ _____

Total Daily Dose/Route _____ _____

Start Date _____ Stop Date _____

Medication _____ _____

Total Daily Dose/Route _____ _____

Start Date _____ Stop Date _____

Please list any other treatment provided: _____

Describe response to treatment: _____

Describe clinical course of events: _____

Were there any unusual features of the patient's clinical course?

_____

Outcome:

Patient's current condition:

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

Date of death (dd/mm/yyyy)_____ Cause of death _____

- ☐ Unknown/ Lost to followup

Was ustekinumab re-administered after the event? ☐ Yes ☐ No

If yes, did TB recur or worsen?

List details: _____

Other information: _____

REPORTER Name:

Address:

City: State/ Province:

Country: Postal Code:

Email:

Phone/Fax: (include country code)

Signature _____ Date _____

Title/Role/Organization _____

Return completed form to Amgen via email: svc-ags-in-us@amgen.com
or fax: 1-888-814-8653

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AMGEN

Ustekinumab Follow-up Questionnaire for Malignancies (Including Lymphoma, Second, and Secondary Malignancies)

Date of this report (dd/mm/yyyy):

AER #:

This form is subject to applicable laws governing the protection of personal information.The information provided on this form may be transferred and processed outside of the country in which it is collected.
Do not provide information by or through which a patient can be identified, other than the specific information required by this form.This prohibition includes, for example, name, address, telephone number, and government issued identifier.

1. PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate dates as dd/mm/yyyy)

Patient Identifier (if using DOB: dd/mmm/yyyy) | Patient initials: | Gender: ☐ Male ☐ Female | Weight: ____ lb ____ kg | Date of event onset (dd/mm/yyyy) | Event reported term | Safety Database No.

Age at time of event: _____ Height: _____

Patient ethnicity: _____ ☐ Unknown

Co-suspect medications (include start and stop date):

2. USTEKINUMAB ADMINISTRATION (Please indicate dates as dd/mm/yyyy)

Indication for use: ☐ Plaque Psoriasis ☐ Psoriatic Arthritis ☐ Crohn's Disease ☐ Ulcerative Colitis ☐ Other _____

Ustekinumab Dose _____ Frequency _____ Route _____

Batch # _____ Exp Date _____ ☐ Unknown Batch #

Ustekinumab Exposure: First administered (start date) _____

Last dose before event (date): _____ Doses given prior to event: _____

Doses were skipped: ☐ No ☐ Yes (specify dates/reason) _____ ☐ Unknown

Ustekinumab discontinued: ☐ No ☐ Yes (specify dates/reason) _____ ☐ Unknown

3. EVALUATIONS AND LABORATORIES AT TIME OF EVENT(S) (Please attach copies of reports, if available)

Diagnostic	Results/Units	Normal Reference Range	Date	Report Attached Y	Report Attached N
WBC with differential					
Lymphocytes					
Neutrophils					
ANC					
Eosinophils					
Hemoglobin					
Hematocrit					
RBC					
Reticulocytes					
Erythrocyte abnormalities					
Platelet count					
Other labs (specify)					

Diagnostic	Results/Units	Normal Reference Range	Date	Report Attached Y	Report Attached N
Immunoglobulin levels:					
IgA					
IgG					
IgM					
LDH					
Fibrinogen					
BUN/Creatine					
Haptoglobin					
ALT/AST					
Alkaline phophatase					
Total protein					
Other labs (specify)					

4. REPORT RESULTS (Indicate date performed dd/mm/yyyy and attach reports if available)

Mammography/breast exam _____ Pap Smear/PSA _____ Pathology reports _____

Sigmoidoscopy/colonoscopy _____ Rectal exam _____ Urinalysis _____

Fecal occult blood _____ MRI/X-rays/CT _____ Other consult reports _____

5. CONCOMITANT MEDICATIONS (Please specify including start and stop date. Include dietary supplements and OTC medications):

Drug name	Indication for use	Dose/Frequency/Route	Start date(dd/mm/yyyy)	Stop date (dd/mm/yyyy)

6. HISTORY OF IMMUNOSUPPRESIVE MEDICATIONS USED TO TREAT THE PATIENT (List others if applicable)

Medication(s)	Used Before Initation of ustekinumab	Used Concomitantly With Ustekinumab	Used After Discontiunation of ustekinumab	Dose, Route and Therapy Dates
Biologic(s) (specify)	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	
Methotrexate	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	
Prednisone	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	
Cyclosporine	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	
Azathioprine	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	
6-Mercaptopurine	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	
Other (specify)	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	

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7. RELEVANT MEDICAL/FAMILY HISTORY (Check all that apply and provide details)

- ☐ Previous malignancy (type, date) _____
- ☐ Smoking (current/previous, specify number packs/years) _____
- ☐ History of excessive alcohol use _____
- ☐ Family history of malignancy (specify in 1st degree relatives) _____
  _____(specify in more distant relatives) _____
- ☐ Occupational/Exposure history _____
- ☐ History of radiation therapy (date. indication, dose)_____
  (specify area treated, radiation induced changes)_____
- ☐ Premalignant lesions (eg, Barrett's, Bowen's, etc)_____
- Viral infections ☐ EBV ☐ HIV ☐ HPV ☐ HBV ☐ HCV
- ☐ Excessive sun exposure (detail)_____
- ☐ History of PUVA (Psoralen + UV-A rays)_____
- ☐ History of TNF blocker therapy (specify drug, dates, total number doses, age at first dose)
  _____
- ☐ History of cytogenetic abnormalities (malignancy, myeloma, germline genetic diseases, etc.)
  _____

8. DIAGNOSIS AND CLASSIFICATION (Please attach reports, if available)

Date of first symptoms _____ Date of diagnosis_____

List signs and symptoms _____

Histopathologic diagnosis (Include report):

_____

Malignancy stage/staging system _____

☐ New primary malignancy ☐ Yes ☐ No ☐ Unknown

Location of malignancy _____

☐ Diagnosis confirmed by biopsy? ☐ Yes ☐ No

Additional diagnostic information, consultation (attach report) _____

Final diagnosis (specify): _____

_____

Lymphoma Classification:

- ☐ Non-Hodgkin's lymphoma: Histologic subtype:_____
  Immunophenotype:_____ Cytogenetics:_____
- ☐ Hodgkin's lymphoma: Histologic subtype:_____
- ☐ Lymphoma tissue tested for Epstein-Barr virus (EBV)? (Please attach report)
  ☐ Yes ☐ No If yes, Test result: ☐ EBV positive ☐ EBV negative
- ☐ Second malignancy (a cancer that is unrelated to the treatment of a prior malignancy and is not a metastasis from the initial malignancy) (List):
- ☐ Secondary malignancy (a cancer caused by treatment of a previous malignancy, eg, treatment with radiation or chemotherapy. It is NOT considered a metastasis of the initial malignancy) (List):

9. TREATMENT, RESPONSE AND OUTCOME (Please indicate dates, attach reports, if available)

Treatment and Response:

How was the patient's malignancy first treated after diagnosis:
(Indicate only the *initial* therapy, not subsequent therapies due to failure, recurrence, etc.)

- ☐ Expectant observation only _____
- ☐ Chemotherapy (list agents) _____
- ☐ Radiation _____
- ☐ Other (specify)_____

Outcome:

Did the event resolve? ☐ Yes ☐ No

If yes, list date resolved (dd/mm/yyyy) _____

Action taken with ustekinumab after event (provide date of action):

- ☐ Discontinued (date) _____
- ☐ Dose interrupted/delayed (date) _____
- ☐ No action taken/dose continued _____

If utekinumab was re-administered after the event, did event recur or worsen?
(provide details) _____

Patient's current condition:

- ☐ Patient is alive with no evidence of malignancy ☐ Unknown
- ☐ Patient is alive, but malignancy is still being treated
- ☐ Patient died: Date of death (dd/mm/yyyy) _____
  Cause of death _____

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Was there evidence that the malignancy spontaneously regressed?:
(ie, regress in the absence of chemotherapy or other treatments) ☐ Yes ☐ No

Response to first treatment for malignancy:

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

Describe clinical course of events:

_____

Describe any unusual features of the patient's clinical course:

_____

Additional comments:

_____

_____

REPORTER Name:

Address:

City: State/ Province:

Country: Postal Code:

Email:

Phone/Fax: (include country code)

Signature_____ Date_____

Title/Role/Organization_____

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AMGEN

Ustekinumab Targeted Follow-up Questionnaire for Cardiovascular Events

Date of this report (dd/mm/yyyy):

AER #:

1. PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate dates as dd/mm/yyyy)

Patient Identifier (if using DOB: dd/mmm/yyyy) | Patient initials: | Gender: ☐ Male ☐ Female | Weight: ____ lb ____ kg | Date of event onset (dd/mm/yyyy) | Event reported term | Safety Database No.

Age at time of event: _____ Height: _____

Co-suspect medications (include start and stop date):

Patient ethnicity: _____ ☐ Unknown

2. USTEKINUMAB ADMINISTRATION (Please indicate dates as dd/mm/yyyy)

Indication for use: ☐ Plaque Psoriasis ☐ Psoriatic Arthritis ☐ Crohn's Disease ☐ Ulcerative Colitis ☐ Other _____

Ustekinumab Dose _____ Frequency _____ Route _____

Batch # _____ Exp Date _____ ☐ Unknown Batch #

Ustekinumab Exposure: First administered (start date) _____

Last dose before event (date): _____ Doses given prior to event: _____

Doses were skipped: ☐ No ☐ Yes (specify dates/reason) _____ ☐ Unknown

Ustekinumab discontinued: ☐ No ☐ Yes (specify dates/reason) _____ ☐ Unknown

3. SIGNS AND SYMPTOMS (Check all that apply, provide timing of symptoms in hours and days in relation to ustekinumab exposure)

Time from injection to onset of symptoms: _____ minutes _____ hours _____ days

☐ Dizziness _____	☐ Facial weakness _____	☐ Extremity paralysis _____	☐ Light-headedness _____
☐ Palpitations _____	☐ Exercise intolerance _____	☐ Chest discomfort _____	☐ Irregular heartbeat _____
☐ Edema _____	☐ Dyspnea _____	☐ Hemoptysis _____	☐ Weakness/fatigue _____
☐ Syncope _____	☐ Cough/Wheezing _____	☐ General malaise _____	☐ Transient weakness _____
☐ Visual disturbance _____	☐ Sweating _____	☐ Nausea/vomiting _____	☐ Sudden death _____
☐ Sensory changes _____	☐ Aphasia _____	☐ Ataxia _____	☐ Other relevant details: _____
☐ Back, neck or jaw pain _____	☐ Left arm pain _____	☐ Altered gait _____	

4. EVALUATIONS AND LABORATORIES AT TIME OF EVENT(S) (List additional details below and attach report(s) if available)

Diagnostic	Results/Units	Normal Reference Range	Date	Report Attached Y	N
Vital signs on initial assessment:					
Blood pressure					
Respiratory rate					
Body temperature					
Heart rate					
O_2 saturation					
Hemoglobin A1C					
Hematocrit					
RBC					
WBC with differential					
Lymphocytes					
Neutrophils					
Eosinophils					
Reticulocytes					
Erythrocyte abnormalities					
Platelet count					
Cardiac enzymes (specify) _____					

Diagnostic	Results/Units	Normal Reference Range	Date	Report Attached Y	N
Total cholesterol					
LDL					
HDL					
Triglycerides					
Fasting glucose					
CRP					
Fibrinogen					
D-Dimer					
BUN/Creatine					
LDH					
Haptoglobin					
ALT/AST					
Alkaline phophatase					
Direct/Total bilirubin					
Arterial blood gases					
Total protein					
Other (specify) _____					

ECG _____

Echocardiogram (ECHO) _____

Chest x-ray _____

MRI _____

CT _____

Cardiac catheterization/angiogram _____

Stress test _____

Multigated acquisition scan _____

Hospital admissions/discharge report _____

Other consult reports (specify) _____

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AMGEN

Ustekinumab Targeted Follow-up Questionnaire for Cardiovascular Events

Date of this report (dd/mm/yyyy): | AER #: |

5. RELEVANT MEDICAL HISTORY (Check all that apply and provide details, dates)

- ☐ Coronary artery disease/Prior MI _____
- ☐ Hypertension _____
- ☐ Hyperlipidemia/Hypercholesterolemia/Hypertriglyceridemia _____
- ☐ Diabetes mellitus _____
- ☐ Obesity _____
- ☐ Peripheral artery disease _____
- ☐ Transient ischemic attack _____
- ☐ Ischemic cerebrovascular accident _____
- ☐ Hemorrhagic cerebrovascular accident _____
- ☐ Congenital heart disease _____
- ☐ Congestive heart failure _____
- ☐ Prior coronary revascularization/Angioplasty _____
- ☐ Arrhythmias _____
- ☐ Cardiomyopathy _____
- ☐ Pericarditis _____
- ☐ Valvular heart disease _____
- ☐ Renal impairment _____
- ☐ Liver disease _____
- ☐ Headaches _____
- ☐ Head trauma _____
- ☐ Smoking (specify number of pack/years) _____
- ☐ Other cardiac disease (specify) _____
- ☐ Other relevant history _____

Relevant family history:

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

6. CONCOMITANT MEDICATIONS (Please specify including start and stop date. Include dietary supplements and OTC medications, attach reports):

Drug name	Indication for use	Dose/Frequency/Route	Start date(dd/mm/yyyy)	Stop date (dd/mm/yyyy)

7. DIAGNOSIS, TREATMENT, RESPONSE AND OUTCOME (Please indicate dates, attach reports, if available)

Diagnosis (details): _____ Date of diagnosis: _____

How was event diagnosed? _____

Treatment and Response:

How was the patient's cardiovascular event first treated after diagnosis?
(Indicate only the ***initial*** therapy, not subsequent therapies due to failure, recurrence, etc.)

_____

Response to first treatment for cardiovascular event:

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

Describe clinical course of events:

_____

_____

Describe any unusual features of the patient's clinical course:

_____

Outcome:

Did the event resolve? ☐ Yes ☐ No

If yes, list date resolved (dd/mm/yyyy) _____

Action taken with ustekinumab after event (provide date of action): ☐ Unknown

- ☐ Discontinued (date) _____
- ☐ Dose interrupted/delayed (date/length of delay) _____
- ☐ No action taken/dose continued _____

Event abate if ustekinumab was withdrawn, interrupted, reduced? ☐ Yes ☐ No ☐ N/A

If ustekinumab was reintroduced, did event recur or worsen? ☐ Yes ☐ No ☐ N/A

(provide details) _____

Causality Assessment: Is the event/reaction related to ustekinumab?

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

Comments: _____

Patient's current condition:

- ☐ Patient is alive with no evidence of cardiovascular event ☐ Unknown
- ☐ Patient is alive, but cardiovascular eventis still being treated
- ☐ Patient died: Date of death (dd/mm/yyyy) _____

Cause of death _____

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or fax: 1-888-814-8653

REPORTER Name:

Address:

City: State/ Province:

Country: Postal Code:

Email:

Phone/Fax: (include country code)

Signature _____ Date _____

Title/Role/Organization _____

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AMGEN

Ustekinumab Targeted Follow-up Questionnaire for Venous Thromboembolism (VTE)

Date of this report (dd/mm/yyyy)

AER #

1. PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate dates as dd/mm/yyyy)

Patient Identifier (if using DOB: dd/mm/yyyy) | Patient initials: | Gender: ☐ Male ☐ Female | Weight: ____ lb ____ kg | Date of event onset (dd/mm/yyyy) | Event reported term | Safety Database No.

Age at time of event: _____ Height: _____

Patient ethnicity: _____ ☐ Unknown

Co-suspect medications (include start and stop date): _____

2. USTEKINUMAB ADMINISTRATION (Please indicate dates as dd/mm/yyyy)

Indication for use: ☐ Plaque Psoriasis ☐ Psoriatic Arthritis ☐ Crohn's Disease ☐ Ulcerative Colitis ☐ Other _____

Ustekinumab Dose _____ Frequency _____ Route _____

Batch # _____ Exp Date _____ ☐ Unknown Batch #

Ustekinumab Exposure: First administered (start date) _____

Last dose before event (date): _____ Doses given prior to event: _____

Doses were skipped: ☐ No ☐ Yes (specify dates/reason) _____ ☐ Unknown

Ustekinumab discontinued: ☐ No ☐ Yes (specify dates/reason) _____ ☐ Unknown

3. CLINICAL SIGNS AND SYMPTOMS (please provide details and dates dd/mm/yyyy)

☐ Leg/Calf edema _____
☐ Leg/Calf pain _____
☐ Chest pain/Discomfort _____
☐ Dyspnoea _____
☐ Tachypnoea _____
☐ Abdominal pain _____
☐ Vomiting _____
☐ Nausea _____
☐ Headache _____
☐ Blurred vision _____
☐ Tachycardia _____
☐ Haemoptysis _____
☐ Syncope _____
☐ Cough _____
☐ Other (specify) _____

4. RELEVANT RESULTS OF DIAGNOSTIC TESTS (including labs, imaging, biopsies, etc.) Detail levels/conclusion, dates, normal ranges, attach reports)

Diagnostic	Results at baseline/prior to use of product (date/value/details)	Results after use of product of product (date/value/details)
CBC w/ smear (microsc eval)		
ESR		
Platelet count		
Antibodies to Platelet Factor 4 (PF4)		
Fibrinogen levels		
Clauss fibrinogen assay		
D-dimer		
Clotting profile (PT, aPTT: before anticoagulation treatment)		
Thrombin time (bovine) plasma		
Prothrombin		
Antithrombin activity		
Factor V Leiden		
Protein C activity		
Protein S activity		
C-reactive protein		
Homocystein levels		
Dilute Russells viper venom time (DRVVFT), 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		

Diagnostic	Results at baseline/prior to use of product (date/value/details)	Results after use of product of product (date/value/details)
Heparin antibodies		
ANA and ANCA		
IL6 levels		
ADAMTS13 activity assay		
Ceruloplasmin		
Direct Coombs test		
Completement C3, C4		
MethylenetetraHydrofolate reductase gene mutation		
Prothrombin gene mutation (G20210A)		
Occult blood in stool		
COVID-19 test		
Troponins		
Brain natriuretic peptide		
Arterial blood gases		
Chest X-ray		
Electrocardiography		
Echocardiography		
Duplex ultrasonography		
MRI scan		
CT scan		
Contrast venography		
Pulmonary angiography		
Ventilation-perfusion scanning		

Other relevant diagnostics/reports, hospital admission/discharge report (details, attach) _____

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5. MEDICAL HISTORY AND CONCURRENT CONDITIONS (Please provide details)

☐ Overweight/Obese (provide height/weight/BMI) _____
☐ Pregnant at time of event (months) _____
☐ Sedentary lifestyle _____
☐ Current/past history of smoking (number of packs/years) _____
☐ Traveling/sitting for long periods of time (> 4 hours) prior to event _____
☐ History of blood transfusion _____
☐ History of cancer _____
☐ History of cardiovascular disorder _____
☐ History of varicose veins, trauma to involved leg/pelvis, DVT/PE/VTE _____
☐ History of autoimmune disease (ie, collagen-vascular disease, IBD) or myeloproliferative disease _____
☐ History of clotting disorder/diagnosis of hypercoagulable state _____
☐ History of organ transplantation? _____

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

Acquired risk factors:

☐ Reduced mobility (paralysis, paresis, travel, etc.) ☐ Inflammatory bowel disease ☐ Recent discontinuation of anticoagulants (eg, heparin, wafarin, DOACs)
☐ Dehydration ☐ Diabetes mellitus ☐ Pregnancy ☐ Postpartum (≤ 3 month after childbirth) ☐ Hormone replacement therapy
☐ Recent surgery ☐ Hypertension ☐ Polycyctic ovary syndrome (PCOS) ☐ Indwelling central venous catheters
☐ Hormonal contraceptives ☐ Hyperlipidemia ☐ Lupus ☐ Myeloproliferative disorders
☐ Phlebitis ☐ Recent trauma ☐ Other significant medical co-morbidities/risk factors for DVT (specify): _____

If yes to any of above provide details: _____ Well's score: _____

6. CONCOMITANT MEDICATIONS

Concomitant Medications (Please specify including start and stop date. Include dietary supplements and OTC medications):

Drug name	Indication for use	Dose/Frequency/Route	Start date(dd/mm/yyyy)	Stop date (dd/mm/yyyy)

7. TREATMENT AND RESPONSE (Please specify patient treatment regimen, response, and outcome of event. Provide dates, attach reports)

Diagnosis: _____ Date of diagnosis: _____

Was patient on VTE prophylaxis? ☐ Yes (specify details) _____ ☐ No

Is the event serious? ☐ Yes ☐ No

If yes, please clarify the seriousness criteria: (provide details)

☐ Caused hospitalization _____ ☐ Was life-threatening _____ ☐ Caused disability _____

☐ Was medically significant _____ ☐ Was fatal (provide date) _____ ☐ Due to congenital anomaly _____

Treatment Regimen After Event (Please specify treatment including start and stop date. Include OTC medications): ☐ Not applicable

Treatment (ie, medication, etc.)	Details (ie, Dose/Frequency/Route)	Response to Treatment	Start date(dd/mm/yyyy)	Stop date (dd/mm/yyyy)

Outcome: ☐ Recovered ☐ Recovering ☐ Not recovered ☐ Fatal ☐ Unknown Provide details/dates: _____

Action taken with ustekinumab following event:

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

Did the event abate after ustekinumab was withdrawn, interrupted, or reduced? ☐ Yes ☐ No

If ustekinumab was reintroduced, did reaction recur? ☐ Yes ☐ No

Causality Assessment:

Is the event/reaction related to ustekinumab? ☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely

Is the event/reaction related to any other condition or medications? (provide details) ☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely

_____

Return completed form to Amgen via email: svc-ags-in-us@amgen.com
or fax: 1-888-814-8653

REPORTER Name:

Address:

City: State/ Province:

Country: Postal Code:

Email:

Phone/Fax: (include country code)

Signature _____ Date _____

Title/Role/Organization _____

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Annex 6. Details of Proposed Additional Risk Minimization Activities (if Applicable)

Not applicable.