EU Risk Management Plan
for
Imuldosa 130 mg concentrate for solution for infusion
Imuldosa 45 mg solution for injection in pre-filled syringe
Imuldosa 90 mg solution for injection in pre-filled syringe
(Ustekinumab)

RMP version to be assessed as part of this application:

RMP Version number	1.2
Data lock point for this RMP	04-Oct-2024
Date of final sign off	04-Oct-2024

Rationale for submitting an updated RMP: This RMP has been updated to align the RMP with the most recent RMP for Stelara, version 30.1 dated 05-Sep-2024 and update the RMP considering the change of indication removing the patented indication of Ulcerative Colitis as per Rapporteurs Day 195 Joint CHMP and PRAC response assessment report (Procedure Number - EMEA/H/C/006221) dated 02-Oct-2024..

Summary of significant changes in this RMP: Significant changes have been made in following sections of RMP: Part I, Part II (Module SVII.3 and SVIII), Part V, Part VI and Part VII (Annex 7 and Annex-8).

Other RMP versions under evaluation: None

Details of the currently approved RMP: None

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QPPV signature: [redacted]

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Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Ustekinumab
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, interleukin inhibitors (L04AC05)
Marketing Authorisation Applicant	Accord Healthcare S. L.U.
Medicinal products to which this RMP refers	03
Invented name(s) in the European Economic area (EEA)	Imuldosa 130 mg concentrate for solution for infusion Imuldosa 45 mg solution for injection in pre-filled syringe Imuldosa 90 mg solution for injection in pre-filled syringe
Marketing authorisation procedure	Centralised Procedure (EMEA/H/C/006221)
Brief description of the product	Chemical class: Monoclonal antibody
	Summary of mode of action: Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12

	or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines participate in immune functions; IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype, IL-23 induces the T helper 17 (Th17) pathway. However, abnormal regulation of IL 12 and IL 23 has been associated with immune mediated diseases, such as psoriasis, psoriatic arthritis, and Crohn's disease. By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis, psoriatic arthritis, and Crohn's disease through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.
	<u>Important information about its composition:</u> *Imuldosa 45 mg solution for injection in pre-filled syringe* Each pre-filled syringe contains 45 mg ustekinumab in 0.5 mL. *Imuldosa 90 mg solution for injection in pre-filled syringe* Each pre-filled syringe contains 90 mg ustekinumab in 1 mL. *Imuldosa 130 mg concentrate for solution for infusion* Each vial contains 130 mg ustekinumab in 26 mL (5 mg/mL). Ustekinumab is a fully human IgG1κ monoclonal antibody to interleukin (IL)-12/23 produced in a murine myeloma cell line using recombinant DNA technology.
Hyperlink to the Product Information	Refer Module 1.3.1 for Product Information
Indication(s) in the EEA	***Current*** **<u>Imuldosa 45 mg/90 mg solution for injection in pre-filled syringe:</u>**

	Plaque psoriasis: Imuldosa 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). *Paediatric plaque psoriasis* Imuldosa is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older with a body weight over 60 kg, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. *Psoriatic arthritis (PsA):* Imuldosa, 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:* Imuldosa 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. **Imuldosa 130 mg concentrate for solution for infusion:** *Crohn's Disease:* Imuldosa 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.
Dosage in the EEA	***Current*** **Posology:**

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

Plaque psoriasis

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

For patients with a body weight > 100 kg the initial dose is 90 mg administered subcutaneously, followed by 90 mg dose 4 weeks later, and then every 12 weeks thereafter. In these patients, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy.

Psoriatic arthritis (PsA):

The recommended posology of Imuldosa is an initial dose of 45 mg administered subcutaneously, followed by 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg.

Paediatric plaque psoriasis (6 years and older)

The recommended dose of Imuldosa for the paediatric population with a body weight over 60 kg is shown in below Table. Imuldosa should be administered at Weeks 0 and 4, then every 12 weeks thereafter.

Body weight at the time of dosing	Recommended Dose
≥ 60-≤ 100 kg	45 mg
> 100 kg	90 mg

There is no dose form for Imuldosa that allows weight-based dosing for paediatric patients below 60 kg. Patients weighing less than 60 kg should be accurately dosed on a mg/kg basis using the solution for injection in vial presentation. Only the patients weighing 60 kg or more may be dosed using a fixed- dose pre-filled syringe.

For paediatric patients weighing less than 60kg, other ustekinumab products offering an option for weight-based dosing should be used instead.

Crohn's Disease:

In the treatment regimen, the first dose of Imuldosa is administered intravenously. For the posology of the intravenous dosing regimen, refer below described posology section of the Imuldosa 130 mg Concentrate for solution for infusion.

The first subcutaneous administration of 90 mg Imuldosa should take place at week 8 after the intravenous dose. After this, dosing every 12 weeks is recommended.

Method of administration:

Imuldosa 45 mg/0.5ml and 90 mg/1 ml pre-filled syringes are for subcutaneous injection only. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

Imuldosa 130 mg concentrate for solution for infusion:

Crohn's Disease

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

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

[a] Approximately 6 mg/kg

The first subcutaneous dose should be given at week 8 following the intravenous dose. For the posology of the subsequent subcutaneous dosing regimen, refer posology section of the Imuldosa solution for injection in pre-filled syringe SmPC.

Method of administration:

Imuldosa 130 mg is for intravenous use only. It should be administered over at least one hour.

Pharmaceutical form(s) and strengths	***Current*** Solution for injection in pre-filled syringe: 45 mg and 90 mg Concentrate for solution for infusion: 130 mg
Is the product subject to additional monitoring in the EEA?	Yes

Part II: Safety specification

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

Not applicable

Module SII - Non-clinical part of the safety specification

Table 2 Non-clinical studies of Imuldosa

Key Safety findings (from non- clinical studies)	Relevance to human usage

A comparative 4-week repeat dose subcutaneous toxicity study of DMB-3115 (*Imuldosa) with Stelara_BS in the Monkey*
Study No.: 8379943
Species: Cynomolgus monkey
Number/Sex/Group: 3 (Male & Female)
Dose: 45 mg/kg/dose administered twice weekly by sub cutaneous route (SC) for 4 weeks
Method of administration: SC injection on the back (Dose Volume: 1 mL/kg)
Toxicity
• **Repeat-dose toxicity studies**
  • None of the samples were found positive for ADA (anti-drug antibody).
  • There was no difference in the toxicity, toxicokinetic or immunogenicity profile of Imuldosa compared to the reference product STELARA.
  • Based on the study finding, dose of 45 mg/kg administered twice weekly by the SC route for 4 weeks was considered to be the no-observed-adverse-effect-level (NOAEL).
	Preclinical data revealed no special hazard likely for humans.

Key Safety findings (from non- clinical studies)	Relevance to human usage
• **Genotoxicity** Genotoxicity studies were not conducted as they are not required for a biosimilar product • **Carcinogenicity** Carcinogenicity studies were not conducted as they are not required for a biosimilar product • **Reproductive and Developmental Toxicity** Reproductive and developmental studies were not conducted as they are not required for a biosimilar product **Safety Pharmacology** Safety pharmacology studies are not required for a biosimilar **Other toxicity-related information or data** Immunogenicity evaluations were performed as a part of a single-dose PK study of Imuldosa and Stelara in Cynomolgus monkey conducted at SC doses of 9 mg/kg. Development of anti-drug antibody (ADA) was also assessed in the 4-week repeat-dose study of Imuldosa and Stelara in Cynomolgus monkey with test and reference item administered twice weekly at doses of 0.9 or 45 mg/kg. In the single-dose pharmacokinetic (PK) study, one animal was found to be ADA positive in each of the two groups administered with different batch of Imuldosa. However, there was no impact of development of ADA on the PK parameters in the study. Presence of ADA was not detected in the 4-week repeat-dose study in Cynomolgus monkeys for any of the groups dosed with of DMB-3115 and Stelara. Animal immunogenicity assessments are conducted to assist in the interpretation of the animal study results and	

Key Safety findings (from non- clinical studies)	Relevance to human usage
generally do not predict potential immune responses to protein products in humans	

Module SIII - Clinical trial exposure

Brief Overview of Development:

Imuldosa has been developed for the treatment of adult and pediatric (≥6 years of age) patients with moderate to severe plaque psoriasis, the treatment of adult patients with active Psoriatic arthritis (PsA), the treatment of adult patients with moderate to severe Crohn's Disease.

Clinical Trial Exposure:

Ustekinumab is dosed for psoriasis and PsA at 0, 4, and 16 weeks and every 12 weeks thereafter. It is assumed that drug exposure occurs up to the time of the next scheduled dose 12 weeks later. The study included 2 periods. In the Period 1 (from Week 0 to Week 28), patients received the assigned treatment (either DMB-3115 or Stelara®) at Weeks 0, 4, and 16. Patients who did not achieve at least PASI 50 response by Week 12 were discontinued from further treatment with ustekinumab (either DMB-3115 or Stelara®). Only those patients who achieved at least PASI 75 response at Week 28 were eligible for inclusion into the Period 2 of the study (Transition period: from Week 28 to Week 52). Exposure to study medication was summarised by body weight (.100 kg and >100 kg) for duration exposure, average dose at week and cumulative number of doses for all weeks for the SAF.

Duration of medication exposure (weeks) = (Date of last study medication administration - Date of first study medication administration+1)/7.

Duration of exposure (days) = Date of last dose of study drug - Date of first dose of study

drug +1.

Weight-based ustekinumab dosages were studied, the standard dosage and the half-standard dosage, as outlined below.

Exposure During Controlled Portions of Clinical Trials

Ustekinumab Dosages in DMB-3115-2		
Subject Body Weight	**Standard Dosage**	**Half-standard Dosage**
≤100 kg	45 mg	22.5 mg
>100 kg	90 mg	45 mg

Clinical Study Design	**Study treatment**	**Comment**
Study No: DMB 3115-1 **Phase 1**, Comparative pharmacokinetic study of ustekinumab biosimilar (DMB-3115 Formulation A), EU-Stelara, and US-Stelara in healthy adult subjects	**Test product:** DMB 3115, contains the active ingredient ustekinumab, is for subcutaneous/IV use, solution for injection in pen device/ conc. solution for infusion. **Reference product:** STELARA® is for Subcutaneous/IV use, solution for injection in pen device/ conc. solution for infusion; marketed by Janssen-Cilag.	**Status: Completed** A total of 645 subjects were screened, of which 300 subjects were randomised and 296 subjects were dosed. Of the 296 subjects, 294 (99.3%) subjects completed the study. Two subjects discontinued the study after the IMP administration
Study No: DMB 3115-2 **Phase III** A randomised, double blind, multicentric, parallel group, and active controlled study comparing efficacy, safety, and immunogenicity of Subcutaneous administration of DMB 3115 (Imuldosa) and EU	**Test product:** DMB 3115, contains the active ingredient ustekinumab, is for subcutaneous/IV use, solution for injection in pen device/ conc. solution for infusion. **Reference product:** STELARA® is for	**Status: Completed** A total of 838 subjects were screened of which 605 subjects were randomis ed and treated: 301 subjects received DMB-3115 and 304 subjects received STELARA. A total of 540 subjects completed Period 1, and 537 of those subjects were re

Clinical Study Design	Study treatment	Comment
sourced STELARA in subjects with moderate to severe psoriasis	Subcutaneous/IV use, solution for injection in pen device/ conc. solution for infusion; marketed by Janssen-Cilag.	randomised in Period 2 as follows: 269 subjects continued to receive DMB-3115, 135 subjects were re randomised to receive STELARA, and 133 subjects were switched to receive DMB-3115.

There were two clinical studies were conducted, one study was Phase 1 studies and a Phase 3 study comparing DMB-3115 with STELARA.

- A Phase 1 clinical study, a single-center, single-dose, randomised, double-blind, 3-arm parallel-group, comparative pharmacokinetic (PK) study of ustekinumab proposed biosimilar (DMB-3115 Formulation A), EU-sourced STELARA (EU-STELARA), and US-sourced STELARA (US-STELARA) in healthy adult subjects (DMB-3115-1).
- A Phase 3 study (DMB-3115-2) comparing the efficacy, safety and immunogenicity of subcutaneous (SC) DMB-3115 and EU-sourced STELARA in patients with moderate to severe chronic plaque psoriasis.

Study DMB-3115-1

Subjects' age ranged from 18 to 55 years, with a mean (SD) of 38.5 (9.89) years. A total of 184 [62.2%] subjects were male and 278 [93.9%] subjects were of White race. Subject characteristics (height, weight, and BMI) were generally well distributed across the treatment groups and were within the predefined limits of the study. Demographic details are presented in below table.

Table 3 Subject Demographics (Safety Analysis Set)

Characteristic	Category	Statistic	DMB-3115 (N = 99)	EU-Stelara (N = 99)	US-Stelara (N = 98)	Overall (N = 296)
Age (years)		n	99	99	98	296
		Mean (SD)	40.5 (9.05)	38.9 (10.33)	36.1 (9.87)	38.5 (9.89)
		Median	40.0	39.0	34.5	38.0
		Q1, Q3	32.0, 49.0	30.0, 48.0	28.0, 45.0	30.0, 47.0
		Min, Max	21, 55	18, 55	20, 55	18, 55

Characteristic	Category	Statistic	DMB-3115 (N = 99)	EU-Stelara (N = 99)	US-Stelara (N = 98)	Overall (N = 296)
Sex	Male	n (%)	59 (59.6)	61 (61.6)	64 (65.3)	184 (62.2)
	Female	n (%)	40 (40.4)	38 (38.4)	34 (34.7)	112 (37.8)
Ethnicity	Hispanic or Latino	n (%)	3 (3.0)	1 (1.0)	2 (2.0)	6 (2.0)
	Not Hispanic or Latino	n (%)	96 (97.0)	98 (99.0)	96 (98.0)	290 (98.0)
Race	White	n (%)	91 (91.9)	94 (94.9)	93 (94.9)	278 (93.9)
	Asian	n (%)	2 (2.0)	2 (2.0)	0	4 (1.4)
	Black or African American	n (%)	1 (1.0)	0	2 (2.0)	3 (1.0)
	American Indian or Alaska Native	n (%)	2 (2.0)	1 (1.0)	1 (1.0)	4 (1.4)
	Native Hawaiian or Other Pacific Islander	n (%)	0	0	0	0
	Other	n (%)	3 (3.0)	2 (2.0)	2 (2.0)	7 (2.4)

N: The number of subjects in the safety analysis set

n: The number of subjects in the specific category

%: Calculated using the number of subjects in the safety analysis set as the denominator (n/(N non-missing)*100)

Study DMB-3115-2

Patient demographics and baseline characteristics in the ITT set are summarised in above table. Majority of the patients across DMB-3115 (67.8%) and Stelara® (71.4%) arms were males and were of White race (DMB-3115: 98.7%; Stelara®: 99.7%). The median (min, max) age and BMI was 45.0 (18.0, 75.0) years and 28.70 (16.7, 52.5) kg/m2, respectively. The mean (SD) duration of plaque type psoriasis was 17.8 (12.26) years and 92.6% of the patients had taken <3 previous systemic therapies for psoriasis. The PGA score of 3 was reported in 475 (78.5%) patients and the PGA score of 4 was reported in 127 (21%) patients. The mean (SD) PASI, PGA, and DLQI scores were 21.36 (8.086), 3.205 (0.4161), and 14.3 (7.24), respectively. A total of 550 (90.9%) were from EU, 21 (3.5%) were from US, and 34 (5.6%) patients were from rest of the world.

Table 4 Demographics and Other Baseline Characteristics (ITT)

Characteristics	Statistic	DMB-3115 (N=301)	Stelara (N=304)	Total (N=605)
Age (Years)				
	Mean	45.4	45.8	45.6
	SD	13.00	13.43	13.21
	Median	45.0	46.0	45.0
	Min, Max	19.0, 73.0	18.0, 75.0	18.0, 75.0
Gender				
Male	n (%)	204(67.8)	217(71.4)	421(69.6)

Characteristics	Statistic	DMB-3115 (N=301)	Stelara (N=304)	Total (N=605)
Female	n (%)	97(32.2)	87(28.6)	184(30.4)
Ethnicity				
Hispanic or Latino	n (%)	3(1.0)	5(1.6)	8(1.3)
Not Hispanic or Latino	n (%)	297(98.7)	299(98.4)	596(98.5)
Not Reported	n (%)	0	0	0
Unknown	n (%)	1(0.3)	0	1(0.2)
Not Applicable	n (%)	0	0	0
Race				
American Indian or Alaska Native	n (%)	0	0	0
Asian	n (%)	3(1.0)	0	3(0.5)
Black or African American	n (%)	1(0.3)	0	1(0.2)
Native Hawaiian or Other Pacific Islander	n (%)	0	0	0
White	n (%)	297(98.7)	303(99.7)	600(99.2)
Multiple[a]	n (%)	0	0	0
Not Reported	n (%)	0	1(0.3)	1(0.2)
Unknown	n (%)	0	0	0

Note: [a] Patients who reported more than 1 race were reported under multiple.

Note: N is the Total number of patients in the ITT in each treatment arm; n is the total number of patients meeting the condition.

Note: Percentages were based on the number of patients in ITT in respective treatment arm (N).

Extent of Exposure (Study DMB-3115-2)

Period 1

The mean duration of treatment exposure was comparable between DMB-3115 and Stelara® arms in patients with body weight ≤100 kg (15.7 weeks versus 15.6 weeks, respectively) and body weight >100 kg (15.8 weeks versus 15.9 weeks, respectively). The cumulative mean number of doses for all weeks was also comparable between DMB-3115 and Stelara® arms (2.9 versus 2.9, respectively).

Period 2

The mean duration of treatment exposure was comparable between DMB-3115, Stelara®, and Stelara® switched to DMB-3115 arms in patients with body weight ≤100 kg (11.9 weeks, 11.9 weeks, and 11.5 weeks, respectively) and body weight >100 kg (11.9 weeks, 12.2 weeks, and 11.8 weeks, respectively). The cumulative mean number of doses for all weeks was 2.0 each for DMB-3115, Stelara®, and Stelara® switch to DMB-3115 arm, respectively.

Table 5 Exposure to Study Intervention (Safety Set)

Study Period 1

		Statistics	DMB-3115 (N=299)	Stelara (N=299)	Total ((N=598)
Body Weight: ≤ 100 Kg	Duration of Exposure (Weeks) [a]	n	215	216	431
		Mean (SD)	15.7 (2.69)	15.6 (2.77	15.7 (2.73)
		Median	16.1	16.1	16.1
		Min, Max	0, 20	0, 19	0, 20
	Dose [45 mg] at Week 0/Day 1	n	215	216	431
		Mean (SD)	45.0 (0.00)	45.0 (0.00)	45.0 (0.00)
		Median	45.0	45.0	45.0
		Min, Max	45, 45	45, 45	45, 45
	Dose [45 mg] at Week 4	n	214	214	428
		Mean (SD)	45.0 (0.00)	45.0 (0.00)	45.0 (0.00)
		Median	45.0	45.0	45.0
		Min, Max	45, 45	45, 45	45, 45
	Dose [45 mg] at Week 16	n	203	205	408
		Mean (SD)	45.0 (0.00)	45.0 (0.00)	45.0 (0.00)
		Median	45.0	45.0	45.0
		Min, Max	45, 45	45, 45	45, 45
	Dose [90 mg] at Week 16	n	1	0	1
		Mean (SD)	90.0 (-)	- (-)	90.0 (-)
		Median	90.0	-	90.0
		Min, Max	90, 90	-	90, 90
Body Weight: >100 Kg	Duration of Exposure (Weeks) [a]	n	84	83	167
		Mean (SD)	15.8 (2.31)	2.13	15.9 ()
		Median	16.1	16.1	16.1
		Min, Max	4, 18	3, 18	3, 18
	Dose [45 mg] at Week 0/Day 1	n	2	0	2
		Mean (SD)	45.0 (0.00)	- (-)	45.0 (0.00)
		Median	45.0	-	45.0
		Min, Max	45, 45	-, -	45, 45
	Dose [90 mg] at Week 0/Day 1	n	82	83	165
		Mean (SD)	90.0 (0.00)	90.0 (0.00)	90.0 (0.00)
		Median	90.0	90.0	90.0

		Statistics	DMB-3115 (N=299)	Stelara (N=299)	Total ((N=598)
		Min, Max	90, 90	90, 90	90, 90
	Dose [45 mg] at Week 4	n	2	0	2
		Mean (SD)	45.0 (0.00)	- (-)	45.0 (0.00)
		Median	45.0	-	45.0
		Min, Max	45, 45	-, -	45, 45
	Dose [90 mg] at Week 4	n	82	83	165
		Mean (SD)	90.0 (0.00)	90.0 (0.00)	90.0 (0.00)
		Median	90.0	90.0	90.0
		Min, Max	90, 90	90, 90	90, 90
	Dose [45 mg] at Week 16	n	2	0	2
		Mean (SD)	45.0 (0.00)	- (-)	45.0 (0.00)
		Median	45.0	-	45.0
		Min, Max	45, 45	-, -	45, 45
	Dose [90 mg] at Week 16	n	79	80	159
		Mean (SD)	90.0 (0.00)	90.0 (0.00)	90.0 (0.00)
		Median	90.0	90.0	90.0
		Min, Max	90, 90	90, 90	90, 90
	Cumulative Number of Doses for All Weeks	n	299	299	598
		Mean (SD)	2.9 (0.23)	2.9 (0.25)	2.9 (0.24)
		Median	3	3	3
		Min, Max	1, 3	1, 3	1, 3

Study Period 2

		Statistics	DMB-3115 (N=267)	Stelara (N=132)	Stelara Switched to DMB-3115 (N=131)	Total ((N=530)
Body Weight: ≤ 100 Kg	Duration of Exposure (Weeks) [a]	n	192	97	91	380
		Mean (SD)	11.9 (2.02)	11.9 (1.49)	11.5 (2.83)	11.8 (2.13)
		Median	12.1	12.1	12.1	12.1
		Min, Max	0, 15	0, 14	0, 14	0, 15
	Dose [45 mg] at Week 28	n	182	92	90	364
		Mean (SD)	45.0 (0.00)	45.0 (0.00)	45.0 (0.00)	45.0 (0.00)
		Median	45.0	45.0	45.0	45.0

		Statistics	DMB-3115 (N=267)	Stelara (N=132)	Stelara Switched to DMB-3115 (N=131)	Total ((N=530)
		Min, Max	45, 45	45, 45	45, 45	45, 45
	Dose [90 mg] at Week 28	n	10	5	1	16
		Mean (SD)	90.0 (0.00)	90.0 (0.00)	90.0 (-)	90.0 (0.00)
		Median	90.0	90.0	90.0	90.0
		Min, Max	90, 90	90, 90	90, 90	90, 90
	Dose [45 mg] at Week 40	n	178	92	85	355
		Mean (SD)	45.0 (0.00)	45.0 (0.00)	45.0 (0.00)	45.0 (0.00)
		Median	45.0	45.0	45.0	45.0
		Min, Max	45, 45	45, 45	45, 45	45, 45
	Dose [90 mg] at Week 40	n	9	4	1	14
		Mean (SD)	90.0 (0.00)	90.0 (0.00)	90.0 (-)	90.0 (0.00)
		Median	90.0	90.0	90.0	90.0
		Min, Max	90, 90	90, 90	90, 90	90, 90
Body Weight: >100 Kg	Duration of Exposure (Weeks) [a]	n	75	35	40	150
		Mean (SD)	11.9 (2.09)	12.2 (0.79)	11.8 (1.95)	11.9 (1.83)
		Median	12.1	12.1	12.1	12.1
		Min, Max	0, 15	9, 14	0, 13	0, 15
	Dose [45 mg] at Week 28	n	3	3	2	8
		Mean (SD)	45.0 (0.00)	45.0 (0.00)	45.0 (0.00)	45.0 (0.00)
		Median	45.0	45.0	45.0	45.0
		Min, Max	45, 45	45, 45	45, 45	45, 45
	Dose [90 mg] at Week 28	n	72	32	38	142
		Mean (SD)	90.0 (0.00)	90.0 (0.00)	90.0 (0.00)	90.0 (0.00)
		Median	90.0	90.0	90.0	90.0
		Min, Max	90, 90	90, 90	90, 90	90, 90
	Dose [45 mg] at Week 40	n	3	3	2	8
		Mean (SD)	45.0 (0.00)	45.0 (0.00)	45.0 (0.00)	45.0 (0.00)
		Median	45.0	45.0	45.0	45.0
		Min, Max	45, 45	45, 45	45, 45	45, 45
	Dose [90 mg] at Week 40	n	70	32	37	139
		Mean (SD)	90.0 (0.00)	90.0 (0.00)	90.0 (0.00)	90.0 (0.00)
		Median	90.0	90.0	90.0	90.0
		Min, Max	90, 90	90, 90	90, 90	90, 90

		Statistics	DMB-3115 (N=267)	Stelara (N=132)	Stelara Switched to DMB-3115 (N=131)	Total ((N=530)
	Cumulative Number of Doses for All Weeks	n	267	132	131	530
		Mean (SD)	2.0 (0.16)	2.0 (0.09)	2.0 (0.21)	2.0 (0.16)
		Median	2	2	2	2
		Min, Max	1, 2	1, 2	1, 2	1, 2

Note: N=Total number of patients in the safety set in each treatment group; n= Total number of patients meeting the condition

Abbreviations: Max= Maximum; Min=Minimum; SD=Standard Deviation.

Note: [a] Duration of medication exposure (weeks)= (Date of last study medication administration – Date of first study medication administration+1)/7.

Note: Minimum duration of exposure is represented as 0 if the patient has not completed 1 week of exposure.

Module SIV - Populations not studied in clinical trials

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

The exclusion criteria of both studies are collectively presented in below table.

Table 6 Exclusion criteria in Phase III Study (DMB-3115-1 and DMB-3115-2)

Important Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rational (if not missing information)
Patients with hypersensitivity to ustekinumab or any of the product excipients	Standard exclusion criteria as per study protocol	No	It is not possible to predict which patients may develop a hypersensitivity reaction to Imuldosa. Imuldosa is contraindicated in patients with a known hypersensitivity to the
Patients who had allergic reaction or hypersensitivity to previous biological treatments.			

Important Exclusion criteria	**Reason for exclusion**	**Is it considered to be included as missing information?**	**Rational (if not missing information)**
			active substance or to any of the excipients.
Previous Medical History: • Patients who received any biological therapeutic agents targeted at inhibiting IL 12 or IL-23, inhibiting IL-17, or integrin. • Patients who received any biological therapeutic agents for psoriasis within past 90 days or within 5 drug half-lives prior to screening, whichever was longer. • Patients who received any monoclonal antibodies within 9 months prior to screening. • Patients who received any other investigational drugs	Standard exclusion criteria as per study protocol	No	For patient's benefit and well-being with drug treatment and also this condition could potentially interfere with the aim of the study.

Important Exclusion criteria	**Reason for exclusion**	**Is it considered to be included as missing information?**	**Rational (if not missing information)**
within 5 half-lives of the investigational treatment prior to investigational product initiation.			
Patients who had an active infection or history of infections as follow: - Any active infection for which systemic anti-infectives were used within 4 weeks prior to IP initiation. - A serious infection, defined as requiring hospitalisation or IV anti-infectives within 8 weeks prior to IP initiation. - Recurrent or chronic infections or other active infection.	Standard exclusion criteria as per study protocol	No	Imuldosa is contraindicated in patients with active infection such as active TB.. Imuldosa may have the potential to increase the risk of infections and reactivate latent infections (SmPC section 4.4
Patients with a known infection with human immunodeficiency virus, hepatitis B, or hepatitis C			Ustekinumab may have the potential to increase the risk of infections

Important Exclusion criteria	**Reason for exclusion**	**Is it considered to be included as missing information?**	**Rational (if not missing information)**
			and reactivate latent infections.
Patients with history or symptoms of active tuberculosis (TB).			Treatment with immunomodulatory agents may increase the risk of infection or worsen an existing infection Imuldosa is contra-indicated in clinically important, active infection.
History of pulmonary infiltrate or pneumonia within 6 months before the date of administration of the IMP.			Treatment with immunomodulatory agents may increase the risk of infection or reactivation an existing infection.
Patients who had an uncontrolled, clinically significant systemic disease such as diabetes mellitus (HbA1c ≥8%), cardiovascular disease including moderate to	Standard exclusion criteria as per study protocol	No	For patient's benefit and well-being with drug treatment and also this condition could potentially interfere

Important Exclusion criteria	**Reason for exclusion**	**Is it considered to be included as missing information?**	**Rational (if not missing information)**
severe heart failure (New York Heart Association class III/IV), renal disease, liver disease or hypertension as assessed by the Investigator			with the aim of the study.
Patients who had neurologic symptoms suggestive of central nervous system demyelinating disease.			
Patients with an active or prior malignancy within 5 years with the exception of treated and cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, OR in situ breast ductal carcinoma.	Standard exclusion criteria as per study protocol	No	For patient's benefit and well-being with drug treatment and also this condition could potentially interfere with the aim of the study.
Patients who received a live or live-attenuated vaccination within 6 weeks prior to the first administration of the investigational product (Day 1). Patient had to	Standard exclusion criteria as per study protocol	No	Administration of live vaccines during immunomodulatory therapy may increase the risk of

Important Exclusion criteria	**Reason for exclusion**	**Is it considered to be included as missing information?**	**Rational (if not missing information)**
agree not to receive a live virus or bacterial vaccination during the study and up to 15 weeks after the last dose of the investigational product.			active infection following vaccination.
Patients who had Bacillus Calmette-Guérin (BCG) vaccination within 1 year prior to the first administration of the IP (Day 1). Patients had to agree not to receive a BCG vaccination during the study and up to 1 year after the last dose of the investigational product	Standard exclusion criteria as per study protocol	No	Administration of live vaccines may increase the risk of active infection following vaccination.

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

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

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

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

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic or renal impairment • Patients with cardiovascular diseases • Immunocompromised patients (due to infections) • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Not included in the clinical development program
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other	Not applicable

Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable as product is not yet launched.

Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable - there is no potential for misuse for illegal purposes.

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

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

- Upper respiratory tract infection, Nasopharyngitis, Local injection site reactions, headache and other GI disorders such as diarrhoea and nausea; Frequency: Common. These events are listed event in Summary of Product Characteristic (SmPC) section 4.8. All are mild in severity and are self-limiting.

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

- None

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

- None

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

- None

Other reasons for considering the risks not important:

- None

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

Table 8: Risks considered important for inclusion in the list of safety concerns in the RMP

Risks considered important for inclusion in the list of safety concerns in the RMP	Risk-Benefit impact
Important Potential Risk	
Serious infections (including mycobacterial and salmonella infections)	Ustekinumab may have the potential to increase the risk of infections and reactivate latent infection. During the clinical studies, there were reported incidence of serious infections (anal abscess and pneumonia), especially in IBD cohort, and serious opportunistic infections (cytomegalovirus colitis & *Listeria monocytogenes*). However, no cases of disseminated Salmonella or atypical mycobacterial infections were observed during clinical trials. If patient develop serious infection, patient should be closely monitored. Prior to initiating treatment with Imuldosa, patients should be evaluated for tuberculosis infection. Uncommon: Cellulitis, dental infections, herpes zoster, lower respiratory tract infection, viral upper respiratory tract infection, vulvovaginal mycotic infection
Malignancy	Immunosuppressants including ustekinumab have the potential to increase the risk of malignancy. Some patients who received ustekinumab in clinical studies developed cutaneous and non-cutaneous malignancies.

	Appearance of multiple cutaneous SCC was found in post-marketing reports who had pre-existing risk factors for developing NMSC. The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, colorectal, melanoma and breast cancers. but they were similar in type and number to those expected in the general US population when adjusted for age, gender and race.
Cardiovascular events	Major adverse cardiovascular events (MACE) are characterised by cardiovascular death, nonfatal myocardial infarction, nonfatal stroke. There is no consistent evidence during clinical studies that ustekinumab increases cardiovascular risk. Patient with high cardiovascular risk should be closely monitored for any cardiovascular event.
Serious depression including suicidality	Psoriasis patients have inherited risk for depression and, in rare cases, suicide. Depression has been identified as an uncommon ADR. Since reported incidence of depression was lower in clinical studies as well as in post-marketing setting across indication and unknown presence of pre-existing psychiatric disease, therefore it is difficult to conclude ustekinumab treatment was associated with an increased risk of depression including suicidal ideation or suicidal attempt (including completed suicide).

Venous thromboembolism	IBD patient has higher risk of developing vascular thrombotic events than in the general population. The incident rates of deep vein thrombosis (DVT) and pulmonary embolism were low and generally similar across treatment groups in clinical trials. There is currently no evidence to suggest biologic plausibility for ustekinumab contributing to the development of thrombosis.
Missing Information	
Long-term safety in pediatric psoriasis patients 6 years and older	The safety of ustekinumab has been studied for up to 60 weeks in pediatric population between 12 and 17 years while for age from 6 to 11 years, treatment duration was for 56 weeks. Since safety profile of ustekinumab in pediatric population has been consistent with adult patient during clinical studies, risk-benefit impact of long-term safety in psoriasis patients 6 years and older is low.
Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	Long-term impact on growth and development in pediatric psoriasis patients 6 years and older is not known.
Long-term safety in adult patients with moderately to severely active Crohn's disease	Long term extension clinical study beyond 03 years in adult patients with moderately to severely active Crohn's disease is not available.

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

Not applicable

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

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

Table 9: Details of important Potential risks

Important Potential risk: Serious infections (including mycobacterial and salmonella infections)	
MedDRA terms (Preferred Terms, or Related Terms)	SOC: Infection and infestation
Potential mechanisms	Studies performed in mice suggest that IL-12 may contribute to protective immune responses to intracellular protozoa, bacteria, and fungal pathogens and IL-23 may contribute to immunity to *Klebsiella pneumonia*, *Mycobacterium tuberculosis, Cryptococcus neoformans*, and *Candida albicans.* Humans who are genetically deficient for IL-12/23p40 or IL-12Rβ1 and who are presumed to be deficient in both IL-12 and IL-23 function have normal resistance to ubiquitous viruses and fungi, gram-positive and gram-negative bacteria, and common opportunistic protozoa. These individuals are susceptible to non-TB primary mycobacteria infection, including BCG, and recurring *Salmonella sp.* Patients with inborn errors of IL-12/23 reportedly developed BCG disease when vaccinated with BCG. They also found that these patients were more susceptible to salmonella infections.[2]
Evidence source(s) and strength of evidence	Published nonclinical and medical literature suggest that inhibition of IL-12/23 may predispose patients to serious infections. 'Serious infection (including

Important Potential risk: Serious infections (including mycobacterial and salmonella infections)	
	mycobacterial and salmonella infections)' is considered an important potential risk with ustekinumab based upon the theoretical risk identified from nonclinical data and in humans who are genetically deficient for the cytokines that are inhibited by ustekinumab (IL-12/23p40 or IL-12Rβ1). However, the risk of developing serious infections (including mycobacterial and salmonella infections) in subjects on anti-IL-12/23p40 therapy such as ustekinumab is currently unknown. Across clinical trials in all indications for which ustekinumab is approved, analysis for serious infections in pooled data during the controlled period does not suggest an increased risk of serious infection in the overall ustekinumab-treated population.
Characterisation of the risk	As per the reference product (STELARA) RMP, based on the review of the safety data to date, no new safety information was identified for the important potential risk of 'Serious infections (including mycobacterial and salmonella infections).' No safety signal has been observed. The impact of serious infection on the individual patient may be significant. Patients with a history of latent TB will require additional therapy prior to using ustekinumab or will have to choose a medication other than ustekinumab. Patients with active infections will have to choose an alternative medication and discontinue use of ustekinumabuntil the infection is cleared. Patients who develop infections may potentially have a more severe course due to use of an immunomodulating agent such as

Important Potential risk: Serious infections (including mycobacterial and salmonella infections)	
	ustekinumab. This important potential risk needs to be carefully weighed against the benefit conferred by use of ustekinumab.
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. **TB:** The most common risk factors for the development of TB include conditions impairing the development of effective cell-mediated immunity to the infection (i.e., advanced age, HIV infection), alcohol abuse, malignancy, corticosteroids or other immunosuppression, connective tissue disease, renal failure, diabetes, and pregnancy. A risk factor for the development of TB is exposure to TB, and patients who were born or lived in countries considered by the World Health Organisation to have a high TB burden (incidence: >300 TB cases/100,000 population/year) or have travelled to these locations may be at higher risk. Exposure in the health care setting or in high-density institutions (i.e., prisons) may also put patients at higher risk of development of TB. The possibility of latent TB must be considered, especially in patients who have immigrated from or travelled to countries with a high prevalence of TB or had close contact with a person with active TB. In patients who are severely ill or immunocompromised, tuberculin tests may yield false negative results.

Important Potential risk: Serious infections (including mycobacterial and salmonella infections)	
	Non-TB mycobacterial (NTM) infections: A retrospective/prospective review performed in Australia, found that significant risks for non-HIV-associated pulmonary Mycobacterium avium/Mycobacterium intracellulare complex (MAC) disease included male sex (OR=2.1; 95% CI: 1.0-4.5) and age >50 years (OR=26.5; 95% CI: 10.9-67.3). Similarly, in a US study including 933 patients with 1 or more NTM isolates, pulmonary disease prevalence was highest in persons aged >50 years (15.5 cases per 100,000 persons). In addition, chronic respiratory disease, especially chronic obstructive pulmonary disease treated with inhaled corticosteroid therapy is a strong risk factor for NTM pulmonary disease. Prolonged occupational exposure to soil was an important risk factor for MAC infection in a US study. **Salmonella:** Factors that could increase risk of salmonella infection include activities that result in close contact with salmonella (eg, international travel, owning a pet bird or reptile) and health issues that weaken resistance to infection (eg, stomach or bowel disorders leading to use of antacids; recent antibiotic use; IBD; or impaired immunity from acquired immune deficiency syndrome, sickle cell disease, malaria, anti-rejection drugs taken after organ transplants, and corticosteroids).[2]
Preventability	Ustekinumab is contraindicated in patients with a clinically important, active infection (eg, active

Important Potential risk: Serious infections (including mycobacterial and salmonella infections)	
	TB) (SmPC section 4.3 [Contraindications]). To prevent serious infections, it is recommended that live vaccines not be given concurrently with Ustekinumab (SmPC sections 4.4 [Special Warnings and Precautions for Use] and 4.5 [Interaction with Other Medicinal Products and Other Forms of Interaction]). For infants exposed to Ustekinumab in utero, administration of live vaccines is not recommended for 6 months following birth or until Ustekinumab infant serum levels are undetectable (SmPC sections 4.4 [Special Warnings and Precautions for Use], 4.5 [Interaction with Other Medicinal Products and Other Forms of Interaction], and 4.6 [Fertility, Pregnancy and Lactation]). *Serious infections:* Caution should be exercised when considering the use of Ustekinumab in patients with a chronic infection or a history of recurrent infection (SmPC section 4.4 [Special Warnings and Precautions for Use]). Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and Ustekinumab should not be administered until the infection resolves. TB: Ustekinumab must not be given to patients with active TB. Ustekinumab should not be given to patients with latent TB unless treatment for latent TB is initiated prior to administering Ustekinumab, including those patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving Ustekinumab should be

Important Potential risk: Serious infections (including mycobacterial and salmonella infections)	
	monitored closely for signs and symptoms of active TB during and after treatment. *NTM infections*: Specific recommendations about the prevention of NTM infections are not available. *Salmonella:* Salmonella infections may result from a variety of sources. Appropriate handling of raw poultry and eggs, avoidance of unpasteurised foods, and handwashing after handling food or animals that may carry salmonella are all means of reducing the risk of developing a salmonella infection.[2]
Impact on the risk-benefit balance of the product	The available cumulative information does not provide evidence for an increased risk of serious infections in patients treated with ustekinumab and therefore a negative impact on the risk-benefit balance of the product is not evident. Further characterisation of the incidence, risk factors, and potential relationships with the use of ustekinumab for serious infections is conducted through routine pharmacovigilance activities.[2]
Public health impact	The potential public health impact is not known.

Important Potential risk: Malignancy	
MedDRA terms (Preferred Terms, or Related Terms)	SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps) SMQ: Malignant tumours (narrow)
Potential mechanisms	Scientific literature suggests that IL-12 can contribute to tumor immunosurveillance and exogenous IL-12 can

Important Potential risk: Malignancy	
	promote tumor-directed cytotoxic T cell responses in tumor vaccine strategies. In contrast, IL-23 has been reported to promote tumor growth in animal models. The preponderance of evidence from the published literature (knockout models where IL-23 is ablated) suggests that a risk for malignancy may actually be reduced in the setting of IL-23 inhibition. However, conflicting data from a limited number of studies in mouse models and from photocarcinogenicity experiments point to an increased risk of malignancy in IL-23p19-deficient mice exposed to UVB radiation. Studies in mice genetically deficient in IL-12, or mice treated with high doses of an anti-mouse IL-12/23p40 antibody, suggest that IL-12 contributes to immunity against certain mouse models of neoplasia. A case of 25-year old patient with IL-12Rβ1 deficiency who developed esophageal carcinoma. However, the contribution of endogenous human IL-12 or IL-23 to tumor immunosurveillance remains unclear.[2]
Evidence source(s) and strength of evidence	There is a theoretical risk of malignancy associated with administration of ustekinumab based on scientific literature pertaining to inhibition of IL-12/23. In the pooled controlled portion of clinical trials across indications, the rate of malignancy other than non-melanoma skin cancer (NMSC) was low and was balanced between the ustekinumab and comparator groups. Since malignancies tend to take a long time to develop, long-term follow up is most relevant. In psoriasis patients treated for up to 5 years of continuous ustekinumab therapy, the risk of malignancies other

Important Potential risk: Malignancy	
	than NMSC was not increased compared with the general US population. Long-term effects of ustekinumab on existing malignancies or in patients with a history of malignancy are not known. In light of the theoretic risk and the longer latency period for the development of malignancy, the topic warrants continued surveillance and malignancy considered an important potential risk.[2]
Characterisation of the risk	As per reference product (STELARA) RMP, Based on the review of the safety data to date, no new safety information was identified for the important potential risk of 'Malignancy.' No safety signal has been observed. As noted above, the incidence of malignancy in ustekinumab clinical trials was consistent with that in the general population.[2] No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving ustekinumab. Thus, caution should be exercised when considering the use of ustekinumab in these patients (SmPC section 4.4 [Special Warnings and Precautions of Use]).[2] The impact of malignancy on the individual patient may be very significant. Patients may potentially have a higher risk of developing malignancies due to use of an immunomodulating agent such as ustekinumab. This important potential risk needs to be carefully weighed against the benefit conferred by use of ustekinumab.[2]
Risk factors and risk groups	Among psoriasis patients, increased risk of solid cancers appears to be related to alcohol drinking and

Important Potential risk: Malignancy	
	cigarette smoking. In addition, exposure to PUVA and immunosuppressants, including cyclosporin and possibly MTX, has been associated with squamous cell carcinoma in psoriasis patients. General risk factors for malignancy include increasing age, lifestyle factors (such as use of alcohol and tobacco and obesity), family history of cancer, and certain environmental exposures. Risk factors for the development of malignancy can differ by cancer site. However, in general, factors that can increase risk of malignancies in Crohn's disease patients include but are not limited to smoking, ongoing inflammation, and carcinogenic effects of immunosuppressive drugs.[2]
Preventability	Predictability and preventability of the development of malignancy is not known. Protection from UV exposure, either solar or from tanning beds may decrease the risk of an individual developing a cutaneous malignancy. caution should be exercised when considering the use of Ustekinumab in patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.[2] All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of non-melanoma skin cancer (SmPC section 4.4 [Special Warnings and Precautions of Use]).

Important Potential risk: Malignancy	
	No testing is available to identify patients at risk for cutaneous malignancy.[2]
Impact on the risk-benefit balance of the product	Although malignancies have been reported in patients treated with ustekinumab in clinical trials and in the postmarketing setting, available cumulative information does not suggest an increased risk of malignancy in patients treated with ustekinumab. Therefore, no negative impact on the risk-benefit balance of the product is evident. Further characterisation of the incidence, risk factors, and potential relationships with the use of Ustekinumab for malignancy is conducted through routine pharmacovigilance activities.[2]
Public health impact	The potential public health impact is not known.

Important Potential risk: Cardiovascular events	
MedDRA terms (Preferred Terms, or Related Terms)	PTs: Acute myocardial infarction, ischemic stroke, thrombotic stroke, Acute coronary syndrome SOC: Cardiac disorders
Potential mechanisms	Patients with severe psoriasis are more likely to demonstrate CV risk factors such as obesity, diabetes, and hypertension when compared with those with no or mild psoriasis. The greatest risk of myocardial infarction (MI) is found in young patients with severe psoriasis. As in psoriasis, patients with PsA are reported to be at increased risk for occlusive vascular diseases, including MI and stroke. The potential mechanistic link between psoriasis and CV events, if any, is unclear.

Important Potential risk: Cardiovascular events	
	Subjects with CD had an overall lower CV risk, based upon baseline CV risk factors, than the psoriasis and PsA populations.[2]
Evidence source(s) and strength of evidence	The risk of developing cardiovascular (CV) events in subjects on anti-IL-12/23p40 therapy such as ustekinumab is currently unknown. A numeric imbalance in rates of investigator reported major adverse cardiovascular event (MACE) was observed between ustekinumab- and placebo-treated subjects in the controlled portions of Phase 2 and Phase 3 trials in psoriasis, resulting predominantly from an imbalance in event rates from a smaller Phase 2 trial. Additional analyses performed by the MAH of the reference product STELARA showed that the overall rates of myocardial infarction and stroke with up to 5 years of treatment with ustekinumab in psoriasis patients are comparable with expected rates in either the general population or in the psoriasis population, and comparable to rates in trials of other biologics. Across indications, analysis of MACE in controlled portions of the pooled clinical trial data does not currently suggest a significant increased risk of MACE in subjects treated with ustekinumab. In summary, the totality of the currently available data does not suggest that ustekinumab increases the risk of MACE; however, in light of the imbalance of CV events in the short-term placebo-controlled portions of the psoriasis clinical trials and the known increased risk of these events in the psoriasis and PsA populations, CV events are considered an important potential risk for ustekinumab.[2]

Important Potential risk: Cardiovascular events	
Characterisation of the risk	As per reference product (STELARA) RMP, based on the review of the safety data to date, no new safety information was identified for the important potential risk of 'Cardiovascular events.' No safety signal has been observed. There is evidence for an increased background risk of CV disease in patients with psoriasis and IBD, and patients may experience debilitating MI, stroke, or death. Patients are not considered at further CV risk from use of ustekinumab beyond that related to the psoriasis or IBD population risk. Patients with psoriasis and IBD require vigilance and adequate treatment of CV risk factors including hypertension, hypercholesterolemia, and diabetes. The impact of MACE on the individual patient is potentially significant. Major adverse cardiovascular events may result in fatal outcome.[2]
Risk factors and risk groups	The risk factors in the development of CV disease are well known and include hypertension, hypercholesterolemia, diabetes, smoking, age, male gender, obesity, and family history. The PsA and the psoriasis populations share certain risk factors such as increased CV risk, increased body weight, and increased BMI, which have also been observed in Crohn's disease patients.[2]
Preventability	The preventability of CV disease is based upon the modification of known risk factors. A relationship between CV events and Ustekinumab has not been established.[2].
Impact on the risk-benefit balance of the product	Although MACE have been reported in patients treated with Ustekinumab in clinical trials and in the post

Important Potential risk: Cardiovascular events	
	marketing setting, the available cumulative information does not provide compelling evidence for an increased risk of MACE in patients treated with Ustekinumab. Therefore, no significant negative impact on the risk-benefit balance of the product is expected.[2].
Public health impact	The potential public health impact is not known.

Important Potential risk: Serious depression including suicidality	
MedDRA terms (Preferred Terms, or Related Terms)	PTs: Depression, Intentional self-injury, Suicide attempt, Completed suicide, Suicidal behaviour, Suicidal ideation SMQ: Depression and suicide/self-injury (broad)
Potential mechanisms	Depression is a complex disease with a variety of biologic theories for the pathophysiology. The mechanism by which Ustekinumab could cause depression is not known.
Evidence source(s) and strength of evidence	Psoriasis patients can have an increased risk for depression and, in rare cases, suicide. Depression has been identified as an ADR for Imuldosa (SmPC section 4.8 [Undesirable Effects] and Package Leaflet section 4) based on a safety signal identified in the placebo-controlled period from the Phase 2 and Phase 3 psoriasis clinical trials. The incidence of serious depression including suicidality across indications remains low.[2] The available safety data from clinical studies and post-marketing experience have not identified a safety signal of suicidal ideation or suicidal attempt (including completed suicide). However, based on the severity of

Important Potential risk: Serious depression including suicidality	
	these events, serious depression including suicidality is considered an important potential risk for ustekinumab.[2]
Characterisation of the risk	As per reference product (STELARA) RMP, based on the review of the safety data to date, no new safety information was identified for the important potential risk of 'Serious depression including suicidality.' No safety signal has been observed. The impact of depression on the individual patient may be very significant, and patients with a history of untreated or inadequately treated depression should be treated for such. There may be psychosocial impact and possibility of death from suicide attempts.[2]
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.[2]
Preventability	There is no known means of preventing depression. Caution should be exercised in patient with baseline risk of depression.
Impact on the risk-benefit balance of the product	Although depression has been reported in patients treated with Ustekinumab in clinical trials and in the post marketing setting, available cumulative information does not provide evidence for an increased risk of depression in patients treated with Ustekinumab. Therefore, no significant negative impact on the risk-benefit balance of the product is evident.

Important Potential risk: Serious depression including suicidality	
	Further characterisation of the incidence, risk factors, and potential relationships with the use of Ustekinumab for depression is conducted through routine pharmacovigilance activities.[2]
Public health impact	The potential public health impact is not known..

Important Potential risk: Venous thromboembolism	
MedDRA terms (Preferred Terms, or Related Terms)	PTs: Deep vein thrombosis, pulmonary embolism, embolism venous SMQ: Embolic and thrombotic events, venous (broad)
Potential mechanisms	Currently, there is no known mechanism by which ustekinumab could induce or exacerbate VTE. The available literature shows that IL-12 and IL-23 are not implicated in the process of venous thrombosis. However, patients with IBD are at higher risk of venous thrombosis. Venous thromboembolism in patients with IBD is a multifactorial event that involves both hereditary (factor V Leiden mutation, G20210A mutation of the prothrombin gene, and homozygous C677T mutation in the methylenetetrahydrofolate reductase gene) and acquired factors (dehydration, indwelling catheters, prolonged immobilisation, hyperhomocysteinemia, surgical interventions, active disease with a high inflammatory burden, hospitalisation, colonic localisation, 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

Important Potential risk: Venous thromboembolism	
	contribute to a higher prothrombotic state. These mechanisms include: • Increased plasma levels of recognised 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 platelet such as thrombocytosis and increased activation and aggregation. Ustekinumab inhibits IL-12/23 and the inhibition of IL-23 is associated with reduced plasma levels of the pro-inflammatory cytokines (TNFα, IL-6, and IL-8) that have been implicated in thrombogenesis. Therefore, currently there is no evidence to suggest biologic plausibility for the inhibition of IL-12/23 contributing to the development of thrombosis.[2]
Evidence source(s) and strength of evidence	Patients with IBD can have an increased risk for blood clots in veins due to their underlying condition and other risk factors (dehydration, use of catheters, prolonged immobilisation, hospitalisation, surgical interventions, oral contraceptive use, etc.). Venous thromboembolism (VTE) was originally identified as an important potential risk based on data

Important Potential risk: Venous thromboembolism	
	collected through 44 weeks of treatment in the ustekinumab Crohn's disease clinical trials. The rate of VTE as measured by the number of cases observed per time of treatment (i.e., per 100 years of treatment of subjects) was approximately twice as high in the ustekinumab group compared with the placebo group, but both rates are within the broad range of incidence rates reported in the literature for IBD. Overall, safety results from the Crohn's disease clinical trials through Week 96, UC trials through Week 44, and from clinical trials conducted for other indications, as well as cumulative post-marketing data, do not indicate an increased rate with ustekinumab treatment.[2]
Characterisation of the risk	As per Reference product (STELARA) RMP, based on the review of the safety data to date, no new safety information was identified for the important potential risk of 'Venous thromboembolism.' No safety signal has been observed. The impact of VTE on the individual patient may be significant and may result in a fatal outcome or cause serious long-term complications. Patients with IBD may require prolonged or indefinite anticoagulant therapy. Patients may experience debilitating VTE events including events of deep vein thrombosis, pulmonary embolism, or splanchnic vein thrombosis with or without fatal outcome. The occurrence of VTE imparts a greater risk of in-hospital mortality among hospitalised IBD patients that is greater than the greater mortality risk imparted by VTE in the non-IBD population. Patients with IBD require vigilance in adequate treatment of VTE risk factors.[2]

Important Potential risk: Venous thromboembolism	
Risk factors and risk groups	Patients suffering from IBD, namely Crohn's disease and UC, are more prone to thromboembolic complications compared with the general population. A study of IBD patients conducted in the UK reported that there was increased risk of VTE during disease flares and chronic activity. In a Danish population study that included children and adults, and the highest risk of VTE was in the 0 to 20 years age group with an HR of 6.6 (95% CI: 3.3 to 13.2), compared with 1.6 (95% CI: 1.5 to 1.8) for the ⩾60 years age group. Risk has also been reported to be greater for males, with an incidence rate of 1.34/1000 PY, than for females with an incidence rate of 0.73/1000 PY. Smoking and the need for steroid treatment have also been shown to be risk factors for VTE with ORs of 3.46 (95% CI 1.14-10.5) and 2.97 (95% CI: 0.99-8.92), respectively.[2]
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 mobilisation after surgery, graduated compression stockings or pneumatic devices, limited and rational use of venous catheters, weight loss, alternative methods of contraception, etc.[2]
Impact on the risk-benefit balance of the product	Although VTE has been reported in patients treated with ustekinumab in clinical trials and in the postmarketing setting, available cumulative information does not provide evidence for causal association between VTE and the use of ustekinumab.

Important Potential risk: Venous thromboembolism	
	Therefore, no significant negative impact on the risk-benefit balance of the product is evident. Further characterisation of the incidence, risk factors, and potential relationships with the use of ustekinumab for VTE is conducted through routine pharmacovigilance activities.[2]
Public health impact	The potential public health impact is not known..

SVII.3.2 Presentation of the missing information

Table 10: Presentation of the missing information

Missing Information: Long-term safety in pediatric psoriasis patients 6 years and older	
MedDRA terms (Preferred Terms, or Related Terms)	PTs: Pustular psoriasis, Guttate psoriasis, Erythrodermic psoriasis, Psoriasis, Nail psoriasis, Paradoxical psoriasis, Rebound psoriasis
Evidence Source	The safety of ustekinumab has been studied in two phase 3 studies of paediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks and the second study was in 44 patients from 6 to 11 years of age treated for up to 56 weeks. In general, the adverse events reported in these two studies with safety data through up to 1 year were similar to those seen in previous studies in adults with plaque psoriasis.
Population in need of further characterisation	Pediatric patients with psoriasis ≥6 years of age with long-term exposure to ustekinumab.
Anticipated risk/consequence of the missing information	Through 01 year of clinical study, safety data identified in pediatric population was comparable with adult

Missing Information: Long-term safety in pediatric psoriasis patients 6 years and older	
	population. Although long-term safety data in paediatric population is not available, the anticipated risk/consequence of use in patients with concurrent malignancy or a history of malignancy is very limited

Missing Information: Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	
MedDRA terms (Preferred Terms, or Related Terms)	PTs: Pustular psoriasis, Guttate psoriasis, Erythrodermic psoriasis, Psoriasis, Nail psoriasis, Paradoxical psoriasis, Rebound psoriasis
Evidence Source	Unlike adult patients, wherein 04-05 years safety & data is available, the currently available safety and efficacy data of ustekinumab use in pediatric psoriasis patients is only for 1 year. Long-term extension study is needed to evaluate impact of ustekinumab used on growth and development in pediatric psoriasis patients of 06 years and older.
Population in need of further characterisation	Pediatric patients with psoriasis ≥6 years of age with long-term exposure to ustekinumab.
Anticipated risk/consequence of the missing information	Given safety data of ustekinumab in pediatric population is comparable with adult patient, the anticipated risk/consequence of this missing information is considered minimal.
Missing Information: Long-term safety in adult patients with moderately to severely active Crohn's disease	
MedDRA terms (Preferred Terms, or Related Terms)	PT: Crohn's disease

Evidence Source	Through week 272 in long-term extension study in Crohn's Disease, safety profile of ustekinumab was consistent with the established safety profile of ustekinumab. However, safety profile beyond 05 years is not yet available.
Population in need of further characterisation	Adults with moderately to severely active CD who have been treated with ustekinumab beyond maintenance Week 272.
Anticipated risk/consequence of the missing information	Based on the consistency of safety profile of ustekinumab used in CD in comparative long-term study (i.e., through 05 years), the anticipated risk/consequence of this missing information is considered minimal.

Module SVIII - Summary of the safety concerns

Table 11: Summary of safety concerns

Important identified risks	• None
Important potential risks	• Serious infections (including mycobacterial and salmonella infections) • Malignancy • Cardiovascular events • Serious depression including suicidality • Venous thromboembolism
Missing information	• Long-term safety in pediatric psoriasis patients 6 years and older

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

Note: Safety concern (missing information) 'Long-term safety in adult patients with moderately to severely active ulcerative colitis' is not considered for IMULDOSA, considering ulcerative colitis is not a proposed indication for IMULDOSA.

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for the mentioned safety concerns.

As part of the routine pharmacovigilance procedures for biologics, information about trade name and batch numbers will be required as part of case validation. As per Accord procedural documents, Accord shall record trade names and batch numbers of any adverse events reported in association with the use of any Imuldosa (Ustekinumab).

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Specific adverse reaction follow-up questionnaires for following risks concerning use of Ustekinumab:
    - Serious infections (including mycobacterial and salmonella infections)
    - Malignancy
    - Cardiovascular events
    - Venous thromboembolism

Purpose: Risk wise description is provided as follows:

- to collect information on serious infections, opportunistic infections and information on tuberculosis
- to collect information on malignancies (including lymphoma, second and secondary malignancies)
- to collect information on cardiovascular events
- to collect information on venous thromboembolism

III.2 Additional pharmacovigilance activities

None proposed

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable

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

V.1. Routine Risk Minimisation Measures

Table 12: Description of routine risk minimisation measures by safety concern

Important potential risk	
Serious infections (including mycobacterial and salmonella infections)	*Routine risk communication:* • SmPC sections 4.3, 4.4, 4.5, 4.6 and 4.8 • PIL section 2 and 4 *Routine risk minimisation 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 ustekinumab, is included in SmPC section 4.4. • Recommendation to monitor patients for signs and symptoms of active TB during and after ustekinumab treatment, is included in SmPC section 4.4. • Guidance for managing patients who develop a serious infection, is included in SmPC section 4.4. • Recommendations regarding the administration of live vaccines to patients receiving ustekinumab and to infants exposed to ustekinumab in utero,

	is included in SmPC section 4.4. (The same recommendations are included in SmPC section 4.5 [Interaction with Other Medicinal Products and Other Forms of Interaction]). • Recommendation regarding the administration of live vaccines to infants exposed to ustekinumab in utero, is included in SmPC section 4.6. • Guidance for patients who have recently had or are going to have a vaccination, is included in PL section 2. • Guidance for mothers who received ustekinumab while pregnant and recommendation regarding the administration of live vaccines to infants exposed to ustekinumab in utero, is included in PL section 2. • 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 ustekinumab, is included in PL section 4. *Other routine risk minimisation beyond product information:*

	• The prescription only status of the product
Malignancy	*Routine risk communication:* • SmPC sections 4.4 and 4.8 • PIL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of non-melanoma skin cancer, are included in section 4.4 of Imuldosa SmPC *Other routine risk minimisation beyond product information:* • The prescription only status of the product
Cardiovascular events	*Routine risk communication:* None *Routine risk minimisation activities recommending specific clinical measures to address the risk:*

	None *Other routine risk minimisation beyond product information:* The prescription only status of the product
Serious depression including suicidality	*Routine risk communication:* • SmPC section 4.8 • PIL section 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* None *Other routine risk minimisation beyond product information:* • The prescription only status of the product
Venous thromboembolism	*Routine risk communication:* None *Routine risk minimisation activities recommending specific clinical measures to address the risk:* None *Other routine risk minimisation beyond product information:* The prescription only status of the product

Missing information	
Long-term safety in pediatric psoriasis patients 6 years and older	*Routine risk communication:* None *Routine risk minimisation activities recommending specific clinical measures to address the risk:* None *Other routine risk minimisation beyond product information:* The prescription only status of the product
Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	*Routine risk communication:* None *Routine risk minimisation activities recommending specific clinical measures to address the risk:* None *Other routine risk minimisation beyond product information:* The prescription only status of the product
Long-term safety in adult patients with moderately to severely active Crohn's disease	*Routine risk communication:* None *Routine risk minimisation activities recommending specific clinical measures to address the risk:*

	None *Other routine risk minimisation beyond product information:* The prescription only status of the product

V.2. Additional Risk Minimisation Measures

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

V.3 Summary of risk minimisation measures

Table 13: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important Potential Risk		
Serious infections (including mycobacterial and salmonella infections)	Routine risk minimisation measures: • SmPC sections 4.4, 4.3 4.5, 4.6 and 4.8 • PIL section 2 and 4 • 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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire for serious infections (including mycobacterial and salmonella infections) Additional pharmacovigilance activity: None

	ustekinumab, is included in SmPC section 4.4. • Recommendation to monitor patients for signs and symptoms of active TB during and after ustekinumab treatment, is included in SmPC section 4.4. • Guidance for managing patients who develop a serious infection, is included in SmPC section 4.4. • Recommendations regarding the administration of live vaccines to patients receiving ustekinumab and to infants exposed to ustekinumab in utero, is included in SmPC section 4.4. (The same recommendations are included in SmPC section 4.5 [Interaction with Other Medicinal Products and Other Forms of Interaction]). • Recommendation regarding the administration of live vaccines to infants exposed to ustekinumab in utero, is included in SmPC section 4.6.	

	• Guidance for patients who have recently had or are going to have a vaccination, is included in PL section 2. • Guidance for mothers who received ustekinumab while pregnant and recommendation regarding the administration of live vaccines to infants exposed to ustekinumab in utero, is included in PL section 2. • 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 ustekinumab, is included in PL section 4. • The prescription only status of the product	

	Additional risk minimisation measures: None	
Malignancy	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8 • PIL section 2 • All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of non-melanoma skin cancer, are included in section 4.4 of Imuldosa SmPC • The prescription only status of the product Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire for malignancy Additional pharmacovigilance activity: None
Cardiovascular events	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse

	• The prescription only status of the product Additional risk minimisation measures: None	reactions reporting and signal detection: Targeted follow-up questionnaire for cardiovascular events Additional pharmacovigilance activity: None
Serious depression including suicidality	Routine risk minimisation measures: • SmPC section 4.8 • PIL section 4 • The prescription only status of the product Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activity: None
Venous thromboembolism	Routine risk minimisation measures: • The prescription only status of the product Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire for venous thromboembolism Additional pharmacovigilance activity:

		None
Missing information		
Long-term safety in pediatric psoriasis patients 6 years and older	Routine risk minimisation measures: • The prescription only status of the product Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activity: None
Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	Routine risk minimisation measures: • The prescription only status of the product Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activity: None
Long-term safety in adult patients with moderately to severely active Crohn's disease	Routine risk minimisation measures: • The prescription only status of the product Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activity: None

Part VI: Summary of the risk management plan

Imuldosa 130 mg concentrate for solution for infusion & Imuldosa 45 mg/ 90 mg solution for injection in pre-filled syringe (Ustekinumab)

This is a summary of the risk management plan (RMP) for Imuldosa 130 mg concentrate for solution for infusion & Imuldosa 45 mg/ 90 mg solution for injection in pre-filled syringe. The RMP details important risks of Imuldosa 130 mg concentrate for solution for infusion & Imuldosa 45 mg/ 90 mg solution for injection in pre-filled syringe, how these risks can be minimised, and how more information will be obtained about Imuldosa 130 mg concentrate for solution for infusion & Imuldosa 45 mg/ 90 mg solution for injection in pre-filled syringe's risks and uncertainties (missing information).

Imuldosa 130 mg concentrate for solution for infusion & Imuldosa 45 mg/ 90 mg solution for injection in pre-filled syringe's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Imuldosa 130 mg concentrate for solution for infusion & Imuldosa 45 mg/ 90 mg solution for injection in pre-filled syringe should be used.

This summary of the RMP for Imuldosa 130 mg concentrate for solution for infusion & Imuldosa 45 mg/ 90 mg solution for injection in pre-filled syringe should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in the future updates of Imuldosa 130 mg concentrate for solution for infusion & Imuldosa 45 mg/ 90 mg solution for injection in pre-filled syringe's RMP.

I. The medicine and what it is used for

Imuldosa 130 mg concentrate for solution for infusion & Imuldosa 45 mg/ 90 mg solution for injection in pre-filled syringe are indicated for the plaque psoriasis, psoriatic arthritis (PsA), pediatric plaque psoriasis, and Crohn's disease.

It contains ustekinumab as the active substance and it is given by the IV or SC route of administration.

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

Important risk of Imuldosa 130 mg concentrate for solution for infusion & Imuldosa 45 mg/ 90 mg solution for injection in pre-filled syringe, together with measures to minimise such risks and the proposed studies for learning more about Imuldosa 130 mg concentrate for solution for infusion & Imuldosa 45 mg/ 90 mg solution for injection in pre-filled syringe's risks, are outlined below.

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

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

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including 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 Imuldosa 130 mg concentrate for solution for infusion & Imuldosa 45 mg/ 90 mg solution for injection in pre-filled syringe is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Imuldosa 130 mg concentrate for solution for infusion & Imuldosa 45 mg/ 90 mg solution for injection in pre-filled syringe are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Imuldosa 130 mg concentrate for solution for infusion & Imuldosa 45 mg/ 90 mg solution for injection in pre-filled syringe. 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 warrant further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine):

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

II.B Summary of important risks

Important Potential risk: Serious infections (including mycobacterial and salmonella infections)	
Evidence for linking the risk to the medicine	Published nonclinical and medical literature suggest that inhibition of IL-12/23 may predispose patients to serious infections. 'Serious infection (including mycobacterial and salmonella infections)' is considered an important potential risk with ustekinumab based upon the theoretical risk identified from nonclinical data and in humans who are genetically deficient for the

	cytokines that are inhibited by ustekinumab (IL-12/23p40 or IL-12Rβ1). However, the risk of developing serious infections (including mycobacterial and salmonella infections) in subjects on anti-IL-12/23p40 therapy such as ustekinumab is currently unknown. Across clinical trials in all indications for which ustekinumab is approved, analysis for serious infections in pooled data during the controlled period does not suggest an increased risk of serious infection in the overall ustekinumab-treated population.[2]
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. **TB:** The most common risk factors for the development of TB include conditions impairing the development of effective cell-mediated immunity to the infection (i.e., advanced age, HIV infection), alcohol abuse, malignancy, corticosteroids or other immunosuppression, connective tissue disease, renal failure, diabetes, and pregnancy. A risk factor for the development of TB is exposure to TB, and patients who were born or lived in countries considered by the World Health Organisation to have a high TB burden (incidence: >300 TB cases/100,000 population/year) or have travelled to these locations may be at higher risk. Exposure in the health care setting or in high-density institutions (i.e., prisons) may also put patients at higher risk of development of TB. The possibility of latent TB must be considered, especially in patients who have

	immigrated from or travelled to countries with a high prevalence of TB or had close contact with a person with active TB. In patients who are severely ill or immunocompromised, tuberculin tests may yield false negative results. **Non-TB mycobacterial (NTM) infections:** A retrospective/prospective review performed in Australia, found that significant risks for non-HIV-associated pulmonary Mycobacterium avium/Mycobacterium intracellulare complex (MAC) disease included male sex (OR=2.1; 95% CI: 1.0-4.5) and age >50 years (OR=26.5; 95% CI: 10.9-67.3). Similarly, in a US study including 933 patients with 1 or more NTM isolates, pulmonary disease prevalence was highest in persons aged >50 years (15.5 cases per 100,000 persons). In addition, chronic respiratory disease, especially chronic obstructive pulmonary disease treated with inhaled corticosteroid therapy is a strong risk factor for NTM pulmonary disease. Prolonged occupational exposure to soil was an important risk factor for MAC infection in a US study. **Salmonella:** Factors that could increase risk of salmonella infection include activities that result in close contact with salmonella (eg, international travel, owning a pet bird or reptile) and health issues that weaken resistance to infection (eg, stomach or bowel disorders leading to use of antacids; recent antibiotic use; IBD; or impaired immunity from acquired immune deficiency syndrome, sickle cell disease, malaria, anti-rejection drugs taken after organ transplants, and corticosteroids).[2]

Risk minimisation measures	<u>Routine risk minimisation measures:</u> • SmPC sections 4.3, 4.4, 4.5, 4.6 and 4.8 • PIL section 2 and 4 • 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 ustekinumab, is included in SmPC section 4.4. • Recommendation to monitor patients for signs and symptoms of active TB during and after ustekinumab treatment, is included in SmPC section 4.4. • Guidance for managing patients who develop a serious infection, is included in SmPC section 4.4. • Recommendations regarding the administration of live vaccines to patients receiving ustekinumab and to infants exposed to ustekinumab in utero, is included in SmPC section 4.4. (The same recommendations are included in SmPC section 4.5 [Interaction with Other Medicinal Products and Other Forms of Interaction]). • Recommendation regarding the administration of live vaccines to infants exposed to ustekinumab in utero, is included in SmPC section 4.6. • Guidance for patients who have recently had or are going to have a vaccination, is included in PL section 2. • Guidance for mothers who received ustekinumab while pregnant and recommendation regarding the administration of live vaccines to infants exposed

	to ustekinumab in utero, is included in PL section 2. • 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 ustekinumab, is included in PL section 4. • The prescription only status of the product Additional risk minimisation measures: None
Important Potential risk: Malignancy	
Evidence for linking the risk to the medicine	There is a theoretical risk of malignancy associated with administration of ustekinumab based on scientific literature pertaining to inhibition of IL-12/23. In the pooled controlled portion of clinical trials across indications, the rate of malignancy other than non-melanoma skin cancer (NMSC) was low and was balanced between the ustekinumab and comparator groups. Since malignancies tend to take a long time to develop, long-term follow up is most relevant. In psoriasis patients treated for up to 5 years of continuous ustekinumab therapy, the risk of malignancies other than NMSC was not increased compared with the general US population. Long-term effects of ustekinumab on existing malignancies or in patients with a history of malignancy

	are not known. In light of the theoretic risk and the longer latency period for the development of malignancy, the topic warrants continued surveillance and malignancy considered an important potential risk.[2]
Risk factors and risk groups	Among psoriasis patients, increased risk of solid cancers appears to be related to alcohol drinking and cigarette smoking. In addition, exposure to PUVA and immunosuppressants, including cyclosporin and possibly MTX, has been associated with squamous cell carcinoma in psoriasis patients. General risk factors for malignancy include increasing age, lifestyle factors (such as use of alcohol and tobacco and obesity), family history of cancer, and certain environmental exposures. Risk factors for the development of malignancy can differ by cancer site. However, in general, factors that can increase risk of malignancies in Crohn's disease patients include but are not limited to smoking, ongoing inflammation, and carcinogenic effects of immunosuppressive drugs.[2]
Risk minimisation measures	<u>Routine risk minimisation measures:</u> • SmPC sections 4.4 and 4.8 • PIL section 2 • All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of non-melanoma skin cancer, are included in section 4.4 of Imuldosa SmPC • The prescription only status of the product <u>Additional risk minimisation measures:</u> None

Important Potential risk: Cardiovascular events	
Evidence for linking the risk to the medicine	The risk of developing cardiovascular (CV) events in subjects on anti-IL-12/23p40 therapy such as ustekinumab is currently unknown. A numeric imbalance in rates of investigator reported major adverse cardiovascular event (MACE) was observed between ustekinumab- and placebo-treated subjects in the controlled portions of Phase 2 and Phase 3 trials in psoriasis, resulting predominantly from an imbalance in event rates from a smaller Phase 2 trial. Additional analyses performed internally by the MAH show that the overall rates of myocardial infarction and stroke with up to 5 years of treatment with ustekinumab in psoriasis patients are comparable with expected rates in either the general population or in the psoriasis population, and comparable to rates in trials of other biologics. Across indications, analysis of MACE in controlled portions of the pooled clinical trial data does not currently suggest a significant increased risk of MACE in subjects treated with ustekinumab. In summary, the totality of the currently available data does not suggest that ustekinumab increases the risk of MACE; however, in light of the imbalance of CV events in the short-term placebo-controlled portions of the psoriasis clinical trials and the known increased risk of these events in the psoriasis and PsA populations, CV events are considered an important potential risk for ustekinumab.[2]
Risk factors and risk groups	The risk factors in the development of CV disease are well known and include hypertension,

	hypercholesterolemia, diabetes, smoking, age, male gender, obesity, and family history. The PsA and the psoriasis populations share certain risk factors such as increased CV risk, increased body weight, and increased BMI, which have also been observed in Crohn's disease patients.[2]
Risk minimisation measures	Routine risk minimisation measures: • The prescription only status of the product Additional risk minimisation measures: None
Important Potential risk: Serious depression including suicidality	
Evidence for linking the risk to the medicine	Psoriasis patients can have an increased risk for depression and, in rare cases, suicide. Depression has been identified as an ADR for Imuldosa (SmPC section 4.8 [Undesirable Effects] and Package Leaflet section 4) based on a safety signal identified in the placebo-controlled period from the Phase 2 and Phase 3 psoriasis clinical trials. The incidence of serious depression including suicidality across indications remains low. The available safety data from clinical studies and postmarketing experience have not identified a safety signal of suicidal ideation or suicidal attempt (including completed suicide). However, based on the severity of these events, serious depression including suicidality is considered an important potential risk for ustekinumab.[2]
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.[2]
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.8 • PIL section 4 • The prescription only status of the product Additional risk minimisation measures: None
Important Potential risk: Venous thromboembolism	
Evidence for linking the risk to the medicine	Patients with IBD can have an increased risk for blood clots in veins due to their underlying condition and other risk factors (dehydration, use of catheters, prolonged immobilisation, hospitalisation, surgical interventions, oral contraceptive use, etc.). VTE was originally identified as an important potential risk based on data collected through 44 weeks of treatment in the ustekinumab Crohn's disease clinical trials. The rate of VTE as measured by the number of cases observed per time of treatment (ie, per 100 years of treatment of subjects) was approximately twice as high in the ustekinumab group compared with the placebo group, but both rates are within the broad range of incidence rates reported in the literature for IBD. Overall, safety results from the Crohn's disease clinical trials through Week 96, ulcerative colitis trials through Week 44, and from clinical trials conducted for other indications, as well as cumulative postmarketing data,

	do not indicate an increased rate with ustekinumab treatment.[2]
Risk factors and risk groups	Patients suffering from IBD, namely Crohn's disease and UC, are more prone to thromboembolic complications compared with the general population. A study of IBD patients conducted in the UK reported that there was increased risk of VTE during disease flares and chronic activity. In a Danish population study that included children and adults, and the highest risk of VTE was in the 0 to 20 years age group with an HR of 6.6 (95% CI: 3.3 to 13.2), compared with 1.6 (95% CI: 1.5 to 1.8) for the ≥60 years age group. Risk has also been reported to be greater for males, with an incidence rate of 1.34/1000 PY, than for females with an incidence rate of 0.73/1000 PY. Smoking and the need for steroid treatment have also been shown to be risk factors for VTE with ORs of 3.46 (95% CI 1.14-10.5) and 2.97 (95% CI: 0.99-8.92), respectively.[2]
Risk minimisation measures	<u>Routine risk minimisation measures:</u> • The prescription only status of the product <u>Additional risk minimisation measures:</u> None
Missing information: Long-term safety in pediatric psoriasis patients 6 years and older	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> • The prescription only status of the product <u>Additional risk minimisation measures:</u> None

Missing information: Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	
Risk minimisation measures	Routine risk minimisation measures: • The prescription only status of the product Additional risk minimisation measures: None
Missing information: Long-term safety in adult patients with moderately to severely active Crohn's disease	
Risk minimisation measures	Routine risk minimisation measures: • The prescription only status of the product Additional risk minimisation measures: None

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Imuldosa 130 mg concentrate for solution for infusion & Imuldosa 45 mg/ 90 mg solution for injection in pre-filled syringe.

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

There are no studies required for Imuldosa 130 mg concentrate for solution for infusion & Imuldosa 45 mg/ 90 mg solution for injection in pre-filled syringe.

Annex 4 - Specific adverse drug reaction follow-up forms

MAH has developed following targeted follow-up questionnaires

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

Targeted Follow Up Questionnaire for Serious Infections and Opportunistic Infections

Manufacturer Control Number: Drug generic (Trade Name)
Date of Report: _____dd/mmm/yyyy

1. MEDICAL HISTORY AND CONCURRENT CONDITIONS:

☐ Prior history of exposure to TB

Details:

☐ Prior history of exposure to Hepatitis B/C

Details:

Details of vaccination history:

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

Details:

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

2. ADVERSE EVENT DETAILS:

☐ The infection was present prior to starting the product.

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

Details

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

Targeted Follow Up Questionnaire for Tuberculosis (TB)

Manufacturer Control Number: Drug generic (Trade Name)

Date of Report: _____dd/mmm/yyyy

1. RELEVANT MEDICAL/OCCUPATIONAL HISTORY: *(Check all that apply and provide details below)*

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

Details:

2. DIAGNOSTICS:

☐ Purified Protein Derivative (PPD) testing was performed. Indicate test used:

☐ Intradermal skin test

☐ Multipuncture skin test

Number of units administered:

PPD result: mm of induration (0, if no induration)

2nd PPD results (If applicable): mm of induration (0, if no induration)

Date of 2nd PPD: [dd-mmm-yyyy]

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

Explain reasons.

☐ The subject had active TB.

☐ Prophylactic therapy was given.

Time elapsed from onset of TB symptoms to institution of treatment:

Types of tuberculosis:

☐ Pulmonary

☐ Extrapulmonary; Location:

☐ Disseminated, Location:

☐ Multi-drug Resistant TB

Other laboratory results:

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

Targeted Follow Up Questionnaire for Malignancies (including Lymphoma, Second and Secondary Malignancies)

Manufacturer Control Number: Drug generic (Trade Name)
Date of Report: _____dd/mmm/yyyy

1. RELEVANT MEDICAL/FAMILY HISTORY: *(Provide prior diagnoses and details for checked items below)*

☐ Previous malignancy (Provide specific diagnosis):
☐ Occupational/Exposure history:
☐ Excessive sun exposure (Describe):
☐ History of PUVA (Psoralen +Ultraviolet-A rays)
☐ History of radiation
Dose of radiation:
Area treated:
Age (or date of therapy) of the patient when they were treated with radiation:
Indication for radiation:
Any radiation induced changes?
☐ Pre-malignant lesions, e.g., Barret's oesophagus, Bowen's disease. Details:

Viral infections:

☐ EBV ☐ HIV ☐ HPV ☐ HBV or HCV

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

☐ Family history of malignancy (Provide specific diagnoses for each)
☐ In first degree relatives:
☐ In more distant relatives:

☐ Previous history of tumour necrosis factor (TNF) blocker therapy (With medication names, dates of exposure and the total number of doses or an approximation):
Age at first exposure to any TNF blocker:

☐ Previous administration of other immunosuppressive medications, antineoplastic medications, or other drugs, which have a risk for malignancy stated in their label. (e.g., other biologics, methotrexate, azathioprine, cyclosporine, 6-mercaptopurine, prednisone, or other)
Include drug indication, dose levels, and treatment duration (e.g., methotrexate, cyclophosphamide, vincristine, doxorubicin, cyclosporine, biologics)

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

☐ Cytogenetic abnormalities detected at any point in time? (Include those relevant for any malignancy including myeloma- this could be germline genetic diseases predisposing for malignancy e.g., Down's syndrome, neurofibromatosis etc, or cytogenetic abnormalities relevant to myeloma)

2. DIAGNOSTICS:

Histopathologic diagnosis (Include the histopathology report):

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

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

☐ Lymphoma

☐ Non-Hodgkin's lymphoma

Histologic subtype: immunophenotype: Cytogenetics:

☐ Hodgkin's lymphoma

Histologic subtype:

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

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

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

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

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

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

3. TREATMENT:

What was the response to the first treatment for malignancy?

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

Targeted Follow Up Questionnaire for Cardiovascular Events

Manufacturer Control Number: Drug generic (Trade Name)

Date of Report: _____dd/mmm/yyyy

1. DRUG DETAILS:

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

Recent **dose change? Details:**

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

Date [dd-mmm-yyyy], Time:

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

Date [dd-mmm-yyyy], Time:

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

Date [dd-mmm-yyyy], Time:

2. RELEVANT MEDICAL HISTORY:

(Provide prior diagnoses relevant laboratory data [including echo and ischemic evaluation], dates, etc. below.)

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

Relevant Family History:

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

3. ADVERSE EVENT: PATIENT'S SYMPTOMS/SIGNS: *(Check all that apply and provide details below)*

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

Targeted follow up questionnaire for Venous Thromboembolism (VTE)

Manufacturer Control Number: Drug generic (Trade Name)
Date of Report: _____dd/mmm/yyyy

1. ADVERSE EVENT DESCRIPTION:

Patient's clinical signs and symptoms

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

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

2. MEDICAL HISTORY AND CONCURRENT CONDITIONS:

Provide details:

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

Genetic risk factors:

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

Acquired risk factors:

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

If yes to any of the above, provide details: _____

Provide Well's score, if calculated: _____

3. RELEVANT RESULTS OF DIAGNOSTIC TESTS INCLUDING LABORATORY TESTS, IMAGING, BIOPSIES, ETC. *(Note the levels/conclusion, date performed, normal ranges as well as any other details. Alternatively, attach full reports of the diagnostic tests.)*

Diagnostic Test	Results at baseline or prior to use of product (Include date and value/details)	Test results after use of product (Include date and value/details}
CBC with smear (microscopic evaluation)		
ESR		
Platelet count		
Antibodies to platelet factor 4 (PF4)		
Fibrinogen levels		
Clauss fibrinogen assay		
D-Dimer		
Clotting Profile (PT, aPTT- prior to an anticoagulation treatment)		
Thrombin time (Bovine) Plasma		
Prothrombin		
Antithrombin activity		
Factor V Leiden		
Protein C activity		
Protein S activity		
C-reactive protein		
Homocystein levels		

Dilute Russells Viper Venom Time (DRVVT), Plasma		
Activated Protein C Resistance V (APCRV), Plasma		
Thrombophilia interpretation		
Anticardiolipin antibodies (lgG and lgM) or beta-2 glycoproteins antibodies		
Antiphospholipid antibodies (lgG and lgM)		
Lupus anticoagulant		
Heparin antibodies		
ANAand ANCA		
IL6 levels		
ADAMTS13 Activity Assay		
Ceruloplasmin		
Direct Coombs test		
Complement C3, C4		
MethylenetetraHydrofolate reductase gene mutation		
Prothrombin gene mutation (G20210A)		
Occult blood in stool		
COVID-19 test		
Troponins		
Brain Natriuretic Peptide		
Arterial Blood Gases		
Chest X-Ray		
Electrocardiography		
Echocardiography		
Duplex Ultrasonography		
MRI scan		
CT scan		
Contrast Venography		
Pulmonary Angiography		
Ventilation-Perfusion Scanning		

Provide details of any additional diagnostic results: