EU Risk Management Plan for Fymskina (ustekinumab)

RMP version to be assessed as part of this application:

RMP Version number: 0.3

Data lock point for this RMP: 28 Apr 2023

Date of final sign-off: 11 Jun 2024Rationale for submitting an updated RMP: Not applicable for initial marketing authorisation application submission

Summary of significant changes in this RMP: Not applicable

QPPV name: Larissa Gutenmacher-Ruf

QPPV signature: The content of this RMP has been reviewed and approved by the marketing authorization applicant’s QPPV. The electronic signature is available on file.

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Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Ustekinumab
Pharmacotherapeutic group(s) (ATC Code)	L04AC05
Marketing Authorisation Applicant	Formycon AG
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	Fymskina
Marketing authorisation procedure	Centralised Procedure
Brief description of the product	Chemical class: Recombinant fully human immunoglobulin G1 (IgG) κ monoclonal antibody (mAb) with an estimated molecular mass that ranges from 148,079 to 149,690 Daltons
	Summary of mode of action: Ustekinumab binds to the p40 subunit shared by interleukin (IL)-12 and IL-23 and prevents their binding to the IL-12Rβ1 receptor protein expressed on the surface of natural killer or T cells. Ustekinumab may exert its clinical effects in psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis through interruption of the T helper (Th) 1 and Th17 cytokine pathways, which are central to the pathology of these diseases.
	Important information about its composition: Ustekinumab is produced in a Chinese hamster ovary cell line using recombinant deoxyribonucleic acid (DNA) technology.
Hyperlink to the Product Information	Module 1.3.1/Summary of Product Characteristics (SmPC), Labelling and Package Leaflet
Indication(s) in the EEA	Current: Plaque psoriasis: Fymskina is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or have a contraindication to, or are intolerant to other systemic therapies including cyclosporin, methotrexate (MTX) or psoralen and ultraviolet A (PUVA).

	Paediatric plaque psoriasis: Fymskina is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, considering the body weight at the time of dosing who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Psoriatic arthritis (PsA): Fymskina, 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 (CD): Fymskina is indicated for the treatment of adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist or have medical contraindications to such therapies. Ulcerative colitis (UC): Fymskina is indicated for the treatment of adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies.
	Proposed: not applicable
Dosage in the EEA	Current: Fymskina is intended for use under the guidance and supervision of physicians experienced in the diagnosis and treatment of conditions for which Fymskina is indicated. Plaque psoriasis The recommended posology of Fymskina is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment. *Patients with body weight > 100 kg* For patients with a body weight > 100 kg, the initial dose is 90 mg administered subcutaneously, followed by a 90 mg dose 4 weeks later, and then every 12 weeks thereafter. In these patients, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy. Psoriatic arthritis (PsA) The recommended posology of Fymskina is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Alternatively, 90 mg may

	be used in patients with a body weight > 100 kg. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment. <u>Paediatric plaque psoriasis (6 years and older)</u> ≥ 60 to < 100 kg: 45 mg > 100 kg: 90 mg The recommended dose of Fymskina should be administered at Weeks 0 and 4, then every 12 weeks thereafter. Note: A suitable presentation of Fymskina, enabling weight-based dosing of paediatric patients below 60 kg body weight, is currently under development. Patients weighing less than 60 kg should be accurately dosed on a mg/kg basis using another ustekinumab product, 45 mg solution for injection in vials offering weight-based dosing instead. <u>Crohn's Disease (CD) and Ulcerative Colitis (UC)</u> Fymskina treatment is to be initiated with a single intravenous (IV) dose based on body weight, followed by subcutaneous (SC) doses. The infusion solution for IV dose is to be composed of the number of vials of Fymskina 130 mg as specified in SmPC Section 4.2 (Posology and Method of Administration). The first SC dose should be taken at week 8 following the IV dose. For the posology of the subsequent SC dosing, see Section 4.2 of the Fymskina solution for injection in the prefilled syringe SmPC. Patients who have not shown adequate response at 8 weeks after the first subcutaneous dose, may receive a second subcutaneous dose at this time. Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks. Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit 16 weeks after the IV induction dose or 16 weeks after switching to the 8-weekly maintenance dose.
	Proposed: not applicable
Pharmaceutical form(s) and strengths	Current: <u>For SC use</u> The solution is clear, colourless to slightly brown-yellow. Solution for injection in pre-filled syringe: 45 mg/0.5 mL and 90 mg/1 mL

	<u>For IV use</u> The solution is clear, colourless to slightly brown-yellow. Concentrate for solution for infusion: 130 mg/26 mL (5 mg/mL)
	Proposed: not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

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

According to Good Pharmacovigilance Practice (GVP) – Module V, this section is not applicable to biosimilar medicinal products.

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

Data from originator:

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

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

Table SII.1: Key safety findings of Stelara from non-clinical studies and relevance to human usage of ustekinumab

Key safety findings (from non-clinical studies)	Relevance to human usage of ustekinumab
Toxicity:	
• Repeat-dose toxicity Non-clinical safety studies showed that ustekinumab was well tolerated in general developmental, and reproductive toxicity studies following weekly IV or twice weekly SC dosing at doses up to 45 mg/kg.	Based on animal studies, there is a large safety margin for humans administered ustekinumab IV and SC (up to 7.5- and 45-fold higher than the human dose, respectively).
• Reproductive toxicity Repeated dose toxicology studies conducted in Cynomolgus monkeys showed no toxicological effects of ustekinumab on reproductive organs. The no-observed-adverse-effect-level (NOAEL) of ustekinumab for general toxicity and reproductive function of male Cynomolgus monkeys was 45 mg/kg, approximately 45-fold higher than the anticipated human dose. In a female fertility study conducted in mice using anti-mouse IL-12/23p40 mAb, no adverse effects on female fertility were identified.	Results of reproductive toxicity studies suggest that administration of ustekinumab is unlikely to adversely affect male or female fertility.
• Developmental toxicity The NOAEL of ustekinumab for maternal toxicity and for development of the conceptus was 45 mg/kg following weekly IV dosing or twice weekly SC dosing of pregnant monkeys, approximately 45-fold higher than the	Results of developmental toxicity studies suggest that administration of ustekinumab will not adversely affect mothers or their offspring.

anticipated human dose.	
• Genotoxicity Genotoxicity studies have not been conducted with ustekinumab. The standard battery of assays recommended for small molecules is primarily designed to detect substances that interact with deoxyribonucleic acid (DNA) and include gene mutations, chromosome aberrations and/or DNA damage and is not applicable to biotechnology-derived pharmaceuticals (ICH S6).	Monoclonal antibodies such as ustekinumab are not expected to pass through the cellular and nuclear membranes of intact cells and interact with DNA or other chromosomal material; therefore, potential genotoxicity is unlikely.
• Carcinogenicity The risk of malignancy is a safety concern for immune modulating drugs in general. Carcinogenicity studies were not conducted with ustekinumab. Direct evaluation or carcinogenic potential of ustekinumab in carcinogenicity studies is precluded by its limited species reactivity. Ustekinumab only binds human and non-human primate IL-12p40 but does not bind to or neutralise IL-12 or IL-23 from mice or rats. There are no validated non-rodent models of carcinogenicity. Studies suggesting malignancy risk from antagonism of IL-12 include experiments using primarily mouse non-clinical tumor models. These studies have typically shown anti-tumor activity of exogenously administered IL-12 (Brunda et al 1993) or demonstrated compromised host defence to neoplasia following either antagonism of rodent IL-12 activity by anti-murine IL-12 antibodies or genetic ablation of IL-12 activity in knockout mice (Airoldi et al 2005). While data from these studies suggest a possible carcinogenic hazard associated with IL-12 antagonism, they are not adequate or validated to support a carcinogenic risk assessment.	There is a theoretical risk of malignancy associated with administration of ustekinumab based on the scientific literature pertaining to antagonism of IL-12/23p40. Malignancy is an important potential risk for ustekinumab.
Other	
• Hepatotoxicity and nephrotoxicity No evidence of hepatotoxicity or nephrotoxicity was observed in toxicity studies based on clinical pathology and histopathology evaluations.	Based on animal studies, there is a large safety margin for humans administered ustekinumab IV and SC (up to 7.5- and 45-fold higher than the human dose, respectively).
• Infection The risk of infection is a safety concern for immune modulating drugs in general. Infection studies were not conducted with ustekinumab because there are no validated non-rodent models of infections in which ustekinumab would have pharmacological activity. Published rodent studies suggesting infection risk from inhibition of Th1 and Th17 indicated that IL-12 and IL-23 may contribute to protective immune response to viral, bacterial, intracellular protozoa, and fungal pathogens (Bowman et al 2006; Torti and Feldman	There is a theoretical risk of infection associated with administration of ustekinumab based on the scientific literature pertaining inhibition of IL-12/23p40. Serious infections (including mycobacterial and salmonella infections) are an important potential risk for ustekinumab.

2007). One of the 16 monkeys in the high-dose (45 mg/kg group) developed bacterial enteritis in Week 26 of the 6-month SC toxicology study. The possibility of ustekinumab-related contribution to this infection could not be excluded.	

Source: Stelara RMP version 27.3 Part II Module SII

Data from the biosimilar:

Non-clinical pharmacology, pharmacokinetics and toxicology of ustekinumab were thoroughly investigated in the development of the reference product Stelara (Stelara EPAR 2009). Sufficient non-clinical and clinical data are published to conclude that Stelara is a biologic drug of low concern.

Due to the overall comparable physicochemical, biophysical and *in vitro* functional characteristics of FYB202 and the reference product Stelara, for FYB202 the extensive non-clinical data available from the development of the reference product Stelara are used, where applicable. An extensive replication of the non-clinical data set available for Stelara was not planned. Additionally, one pharmacokinetic (PK) study in Göttingen minipigs was conducted for FYB202 in which the pharmacokinetic properties of FYB202 were similar to those of EU-approved Stelara and US-licensed Stelara.

Summary of non-clinical safety concerns

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

Part II: Module SIII - Clinical trial exposure

One comparative clinical trial in 392 patients with moderate-to-severe plaque psoriasis (more trial details see further below) was performed to show comparable efficacy and safety between the biosimilar and the reference product. Two clinical trials in healthy volunteers were performed to evaluate pharmacokinetics using a single dose.

In line with the concept of biosimilarity, the clinical exposure information collected with the originator product is relevant also to the biosimilar and is thus included as valuable information.

Data from the originator:

This subsection provides an overview on the drug exposure from the originator's clinical trials, pooled for all clinical trials in adult and paediatric patients, including all indications (psoriasis in adult and paediatric patients, PsA, Crohn's disease, ulcerative colitis) as presented in the Stelara EU RMP version 27.3. In the following table data for all clinical trials is presented by exposure characteristic.

Table SIII.1: Summary of subject exposure to ustekinumab in all clinical trials including all indications by duration of exposure, age groups, dosage, and race; cumulative up to 11 February 2022

Exposure characteristic	Subjects treated	Total subject-years of follow-up
Duration of exposure (from first to last ustekinumab administration at least)	7561	16319
≥ 6 months (≥14 weeks)	5007	14797
≥ 1 year (≥38 weeks)	3892	13898
≥ 2 years (≥88 weeks)	2892	12502
≥ 3 years (≥140 weeks)	2386	11360
≥ 4 years (≥192 weeks)	2194	10689
≥ 5 years (≥240 weeks)	1148	5861
Age in years		
≥ 6 to < 12	17 M / 27 F	32 M / 59 F
≥ 12 to ≤ 15	26 M / 29 F	25 M / 32 F
> 15 to < 18	28 M / 27 F	29 M / 26 F
≥ 18 to < 45	2349 M / 1574 F	5091 M / 3105 F
≥ 45 to < 65	1902 M / 1198 F	4522 M / 2621 F
≥ 65	218 M / 166 F	439 M / 338 F
Dosage		
Standard dosage [a]	98	147
Half-standard dosage [a]	56	56
0.09 mg/kg	4	1
0.27 mg/kg	9	3
0.675 mg/kg	4	2
0.9 mg/kg	5	2
1.0 mg/kg	130	51
1.35 mg/kg	4	2
2.7 mg/kg	4	2
3.0 mg/kg	133	51
4.5 mg/kg	64	28

Exposure characteristic	Subjects treated	Total subject-years of follow-up
6.0 mg/kg	1105	537
45 mg	2409	4891
63 mg	116	64
90 mg	4227	10057
130 mg	1075	386
270 mg	85	40
Race		
White	6236	14190
Black or African American	140	287
Asian	787	1156
American Indian or Alaskan native	4	4
Native Hawaiian or other Pacific Islander	2	3
Other	173	350
Unknown	8	10
Not reported	56	119

M = male, F = female

[a] subject's body weight ≤60 kg standard dose 0.75 mg/kg, half-standard dose 0.375 mg/kg; >60 kg through ≤100 kg standard dose 45 mg, half-standard dose 22.5 mg; >100 kg standard dose 90 mg, half-standard dose 45 mg.

Source: RMP Stelara (ustekinumab) Version 27.3, Tables SIII.5 to SIII.8

Data from the biosimilar:

The comparative clinical trial (FYB202-03-01) is a multicentre, double-blind, parallel-group, randomised Phase 3 study designed to demonstrate the clinical similarity of FYB202 compared with Stelara in patients with moderate-to-severe plaque psoriasis with regard to efficacy, safety and immunogenicity.

All eligible patients were randomised 1:1 to receive subcutaneous injections of either FYB202 or Stelara 45 mg at Weeks 0 and 4 and at 12-week intervals thereafter (Weeks 16, 28, and 40); the end-of-study visit took place at Week 52. Randomisation was stratified by prior inadequate response or intolerance to a systemic biological treatment in the opinion of the investigator. At Week 28, after receiving treatment at Week 0, 4 and 16, the patients were assessed for PASI response. Patients not achieving a ≥75% improvement from baseline in PASI score (PASI 75) at Week 28 (estimated approximately 30% of patients) were considered non-responders. Non-responders were discontinued from study intervention, but were to be followed until end-of-study and underwent all study-related assessments. Before the Week 28 administration of study intervention, the responding patients were re-randomised in a blinded fashion. Patients, initially randomised to the Stelara treatment arm were re-randomised 1:1, so that 50% of the patients in the original Stelara arm received FYB202 and 50% continued with Stelara. Patients originally randomised to FYB202 continued with FYB202. Patients were treated with 45 mg ustekinumab injections in both groups. Five injections were planned, at Week 0, 4, 16, 28, 40.

392 patients were enrolled, randomised and treated, 197 patients in the FYB202 group and 195 patients in the Stelara group. The study was conducted at 27 sites in 4 countries: Estonia (23 [5.9%] patients), Georgia (49 [12.5%] patients), Poland (212 [54.1%] patients) and Ukraine (108 [27.6%] patients). The safety set (SAF) comprises all patients treated with study medication at least once. The

re-randomised analysis set (RRAS) consists of all patients who were re-randomised and treated with study medication at least once at week 28 or later. Duration of exposure was calculated as: last injection minus first injection date +1; if this duration was <84 days = 12 weeks, then the duration of exposure in patient years = difference / 365 years; if this duration was ≥84 days = 12 weeks, then the duration of exposure = difference + 84 days.

The two PK clinical trials (the definitive PK study FYB202-01-02 and the supportive PK study FYB202-01-01) are randomised, double-blind, single-dose, 3-arm, parallel-group phase 1 study designed to demonstrate pharmacokinetic equivalence of FYB202, EU-approved Stelara and US-licensed Stelara administered as a single subcutaneous injection of 45 mg ustekinumab to healthy volunteers. The pooled SAF comprises 806 healthy subjects (FYB202-01-02, SAF N=492; FYB202-01-01, SAF N=315).

Exposure by age group and gender

The following tables show exposure by number of injections, by age group and gender for mild-to-moderate plaque psoriasis patients and pooled healthy volunteers. For patients, also the duration of exposure is given.

Table SIII.2: Total number of injections administered before Week 28 in patients with moderate-to-severe plaque psoriasis - SAF of Study FYB202-03-01

No. of injections	**FYB202 (N=197) n (%)**	**Stelara EU (N=195) n (%)**	**Total (N=392) n (%)**
1	3 (1.5)[a]	0	3 (0.8)
2	0	3 (1.5)[b]	3 (0.8)
3	194 (98.5)	192 (98.5)	386 (98.5)

SAF = safety analysis set
SC doses of 45 mg ustekinumab Week 0 (1st injection), Week 4 (2nd injection), Week 16 (3rd injection)
[a] 3 patients received FYB202 only at Week 0.
[b] 3 patients received Stelara EU only at Weeks 0 and 4.

Source: FYB202-03-01 CSR Table 14.3.1.1

Table SIII.3: Total number of injections administered after Week 28 in patients with moderate-to-severe plaque psoriasis - RRAS of Study FYB202-03-01

No. of injections	**FYB202-FYB202 (N=189) n (%)**	**Stelara EU-Stelara EU (N=97) N (%)**	**Stelara EU-FYB202 (N=89) n (%)**	**Total (N=375) n (%)**
1	0	0	0	0
2	189 (100.0)[a]	97 (100.0)[a]	89 (100.0)[a]	375 (100.0)[a]

RRAS = re-randomised set
SC doses of 45 mg ustekinumab Week 28 (4th injection), Week 40 (5th injection)
[a] 189 (100.0%) in the FYB202-FYB202 group, 96 (99.0%) in the Stelara EU-Stelara EU group, 89 (100.0%) in the Stelara EU-FYB202 group, and 374 (99.7%) in the total group received all 5 scheduled injections.

Source: FYB202-03-01 CSR Table 14.3.1.2

Table SIII.4: Total number of single subcutaneous injections of 45 mg ustekinumab in healthy volunteers – SAF (N=315) of Study FYB202-01-01 and SAF (N=491) of FYB202-01-02, data pooled

No. of injections	**FYB202 (N=269)**	**Stelara EU (N=268)**	**Stelara US (N=269)**	**Total (N=806)**

	n (%)	n (%)	n (%)	n (%)
1	269 (100.0)	268 (100.0)	269 (100.0)	806 (100.0)

SAF = safety analysis set
Single SC doses of 45 mg ustekinumab

Source: derived from Integrated Safety Analysis, Final v01, 07 July 2023, Table 1.1.1

Table SIII.5: Exposure by age group and gender in patients with moderate-to-severe plaque psoriasis administered FYB202, SAF of Study FYB202-03-01

		Male		Female	
Treatment	**Age range**	**Treated n (%)**	**Patient years**	**Treated n (%)**	**Patient years**
FYB202 throughout the study (N=197)	≥18 – <45	73 (37.1)	72.101	48 (24.4)	47.064
	≥45 – <65	40 (20.3)	38.122	25 (12.7)	24.074
	≥65*	4 (2.0)	4.014	7 (3.6)	6.505
	Total	117 (59.4)	114.237	80 (40.6)	77.643
FYB202 from re-randomisation (N=89)	≥18 – <45	35 (39.3)	15.044	15 (16.9)	5.454
	≥45 – <65	14 (15.7)	5.544	17 (19.1)	7.893
	≥65*	3 (3.4)	1.399	5 (5.6)	2.081
	Total	52 (58.4)	21.988	37 (41.6)	15.428
Total (N=286)	≥18 – <45	108 (37.8)	87.146	63 (22.0)	52.517
	≥45 – <65	54 (18.9)	43.666	42 (14.7)	31.967
	≥65*	7 (2.4)	5.413	12 (4.2)	8.586
	Total	169 (59.1)	136.225	117 (40.9)	93.070

SAF = safety analysis set
*One patient was older than 75 years

Source: Integrated Safety Analysis, Final v01, 07 July 2023, Table 2.1.1

Table SIII.6: Exposure by age group and gender in patients with moderate-to-severe plaque psoriasis administered Stelara EU, SAF of Study FYB202-03-01

		Male		Female	
Treatment	**Age range**	**Treated n (%)**	**Patient years**	**Treated n (%)**	**Patient years**
Stelara EU throughout the study (N=106)	≥18 – <45	41 (38.7)	37.363	27 (25.5)	26.954
	≥45 – <65	21 (19.8)	20.027	12 (11.3)	11.592
	≥65*	3 (2.8)	2.990	2 (1.9)	1.990
	Total	65 (61.3)	60.381	41 (38.7)	40.537
Stelara EU until re-randomisation (N=89)	≥18 – <45	35 (39.3)	18.902	15 (16.9)	8.082
	≥45 – <65	14 (15.7)	7.537	17 (19.1)	9.202
	≥65*	3 (3.4)	1.618	5 (5.6)	2.691
	Total	52 (58.4	28.057	37 (41.6)	19.975
Total (N=195)	≥18 – <45	76 (39.0)	56.266	42 (21.5)	35.036
	≥45 – <65	35 (17.9)	27.565	29 (14.9)	20.794
	≥65*	6 (3.1)	4.608	7 (3.6)	4.682
	Total	117 (60.0)	88.438	78 (40.0)	60.512

SAF = safety analysis set
*One patient was older than 75 years

Source: Integrated Safety Analysis, Final v01, 07 July 2023, Table 2.1.1

Table SIII.7: Age group and gender in healthy volunteer – SAF (N=315) of Study FYB202-01-01 and SAF of Study FYB202-01-02 (N=491), data pooled

		Male	Female
Treatment	**Age range**	**Treated n (%)**	**Treated n (%)**
FYB202 (N=269)	≥18 – <45	108 (40.1)	83 (30.9)
	≥45 – <65	35 (13.0)	43 (16.0)
	Total	143 (53.2)	126 (46.8)
Stelara EU (N=268)	≥18 – <45	103 (38.4)	95 (35.4)
	≥45 – <65	39 (14.6)	31 (11.6)
	Total	142 (53.0)	126 (47.0)
Stelara US (N=269)	≥18 – <45	96 (35.7)	93 (34.6)
	≥45 – <65	46 (17.1)	34 (12.6)
	Total	142 (52.8)	127 (47.2)
Total (N=806)	≥18 – <45	307 (38.1)	271 (33.6)
	≥45 – <65	120 (14.9)	108 (13.4)
	Total	427 (53.0)	379 (47.0)

SAF = safety analysis set

Source: Integrated Safety Analysis, Final v01, 07 July 2023, Table 1.1.1

Exposure by race

In Study FYB202-03-01 (N=392), all patients were white.

In Study FYB202-01-02 and Study FYB202-01-01 (N=806), 791 healthy volunteers were white, thereof 1 of Japanese ethnicity, 9 black, and 6 subjects Asian.

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

The results of the FYB202-03-01 study, which was conducted in adult patients with moderate to severe plaque psoriasis, demonstrate comparative efficacy and safety compared to the reference medicinal product. Ustekinumab effectively neutralises IL-12- and IL-23-mediated functional responses. Abnormal regulation of IL-13 and IL-13 has been associated with a variety of immune-mediated human diseases, including psoriasis, PsA, CD and UC (Benson et al 2011). The originator Stelara is approved for the treatment of moderate-to-severe plaque psoriasis in adults, children and adolescents, PsA, CD and UC (Stelara SmPC 07/2023). In compliance with the requirements for extrapolation to other indications of the reference medicinal product (EMA/CHMP/BMWP/403543/2010), the results of the FYB202-03-01 study contribute at the clinical level to extrapolation to the originator's indications that have not been specifically studied in the clinical development of FYB202.

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

Important exclusion criteria of Study FYB202-03-01 in patients with moderate-to-severe plaque psoriasis are discussed in the following table. Analogue important exclusion criteria were included in the PK studies (FYB202-01-02 and FYB202-01-01), if applicable.

Exclusion criteria in pivotal clinical studies within the development programme

Criterion 1	**Patients with a known history of hypersensitivity to (ustekinumab or) any of the excipients of FYB202 or Stelara**
Reason for being an exclusion criterion	Patients with a history of (immediate) hypersensitivity to ustekinumab or any excipient used were excluded from FYB202 trials to avoid potentially life-threatening hypersensitivity reactions.
Considered to be included as missing information (Yes/No)?	No.
Rationale (if not included as missing information)	'Serious systemic hypersensitivity reactions' is an important identified risk for FYB202. It is not possible to predict which patients may develop a hypersensitivity reaction to FYB202. FYB202 is contraindicated in patients with a known hypersensitivity to the active substance or to any of the excipients (SmPC section 4.3 [Contraindications]). Additional information regarding hypersensitivity reactions that may occur during treatment with FYB202 is provided in SmPC section 4.4 (Special Warnings and Precautions for Use).
Criterion 2	**Patients with active infection or history of infections as follows:** **Any active infection for which systemic anti-infectives were used within 4 weeks prior to randomisation** **A serious infection, defined as requiring hospitalisation or intravenous anti-infectives, within 8 weeks prior to randomisation** **Evidence of any clinically relevant bacterial, viral, fungal, or parasitic infection** **Recurrent or chronic infections or other active infection that, in the opinion of the investigator, might cause this study to be detrimental to the patient**
Reason for being an exclusion criterion	Treatment with immunomodulatory agents may increase the risk of infection, reactivation of a latent infection or worsening of an existing infection.

Considered to be included as missing information (Yes/No)?	No.
Rationale (if not included as missing information)	'Serious infections' (including mycobacterial and salmonella infections) is an important potential risk for FYB202. FYB202 is contraindicated in patients with clinically important, active infection such as active tuberculosis (TB) (SmPC section 4.3 [Contraindications]). Clinical experience suggests the immunosuppression seen with ustekinumab is minimal; however, the SmPC notes that caution should be exercised when considering the use of ustekinumab in patients with a chronic infection or a history of recurrent infection. FYB202 may have the potential to increase the risk of infections and reactivate latent infections (SmPC section 4.4 [Special Warnings and Precautions for Use]). Guidance for the management of subjects who develop infections while being treated with FYB202 is provided in SmPC section 4.4 (Special Warnings and Precautions for Use). While herpes zoster has been recognised as an adverse drug reaction (ADR) for ustekinumab, there has been no evidence of clinically severe presentations, frequent dissemination or increased reactivations in clinical experience.
Criterion 3	**Pregnant or nursing (lactating) women**
Reason for being an exclusion criterion	Per ICH guidance, pregnant women are excluded from clinical trials. Ustekinumab was detected in breast milk of ustekinumab-exposed breast-feeding women (Saito et al 2022).
Considered to be included as missing information (Yes/No)?	No.
Rationale (if not included as missing information)	'Exposure during pregnancy' is an important potential risk for FYB202. The SmPC section 4.6 (Fertility, Pregnancy and Lactation) notes lack of adequate data regarding the use of ustekinumab in pregnant women, advises against the use during pregnancy, and advises for the use of contraception during treatment and up to 15 weeks after treatment.
Criterion 4	**Patients with history of malignancy (EXCEPT**

	basal cell carcinoma treated at least 5 years prior to screening and no evidence of recurrence in the past 12 weeks)
Reason for being an exclusion criterion	Treatment with an immunomodulatory agent may theoretically increase the risk of developing a malignancy. Therefore, patients with malignancy were excluded.
Considered to be included as missing information (Yes/No)?	No.
Rationale (if not included as missing information)	A theoretical risk was recognised based on non-clinical data demonstrating anti IL-12 activity in mice. Therefore, patients with malignancy were excluded.
Criterion 5	**Patients who received bacille Calmette-Guerin (BCG) vaccine within 1 year prior to screening or who plan to receive BCG vaccine during the study period or within 1 year following discontinuation of treatment.**
Criterion 6	**Patients who had received or planned to receive live viral or live bacterial vaccination within 4 weeks prior to randomisation, during the study period, or within 15 weeks after treatment discontinuation.**
Reason for being an exclusion criterion	Administration of live vaccines during immunomodulatory therapy may increase the risk of active infection following vaccination.
Considered to be included as missing information (Yes/No)?	No.
Rationale (if not included as missing information)	Clinical experience suggests the immunosuppression seen with ustekinumab is minimal; however, the SmPC recommends that before live viral or live bacterial vaccination, treatment with FYB202 should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination (SmPC section 4.4 [Special Warnings and Precautions for Use]).
Criterion 7	**Patients with uncontrolled, clinically significant disease such as diabetes mellitus, cardiovascular disease, renal failure, liver disease, or hypertension.**
Criterion 8	**Patients with active neurological disease**

Criterion 9	**such as multiple sclerosis, Guillain-Barre syndrome, optic neuritis, transverse myelitis, or history of neurologic symptoms suggestive of central nervous system demyelinating disease.** **Patients with moderate to severe heart failure (New York Heart Association class III/IV).**
Reason for being an exclusion criterion	These are typical, prudent, precautionary measures applied to clinical trials with investigational medicinal products.
Considered to be included as missing information (Yes/No)?	No.
Rationale (if not included as missing information)	The focus of the study in moderate-to-severe plaque psoriasis patients was to show clinical similarity in a well-defined population as part of the biosimilarity exercise. Thus, it was not intended to investigate psoriasis patients with severe uncontrolled/active concomitant diseases.

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

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, 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 SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women Breastfeeding women	Not included in the clinical development program. Originator: Cumulatively up to 31 December 2021, a total of 102 pregnancies through maternal exposure and 81 pregnancies through paternal exposure were reported from clinical trials. FYB202 clinical trial development programme: 4 accidental pregnancies through maternal exposure were reported, 1 in a subject in Study FYB202-03-01 (Stelara EU-FYB202 group) and 3 in Study FY202-01-02 (1 treated with Stelara-EU, 1 with Stelara-US, and 1 with FYB202).

Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme.
Population with relevant different ethnic origin	Originator: The majority of subjects were white (84%) and Asian (11%). FYB202: In the study in patient with moderate-to severe plaque psoriasis, all patients were white. In the studies in healthy volunteers, most subjects were white (98%).
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other: paediatric patients	Originator: Exposure in paediatric patients is presented in Table SIII.1.

For originator source: Stelara RMP v27.3

Summary of missing information due to limitations of the clinical development program

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

Part II: Module SV - Post-authorisation experience

Not applicable.

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

Potential for misuse for illegal purposes

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

Part II: Module SVII - Identified and potential risks

FYB202 and the reference product Stelara were well tolerated in Study FYB202-03-01 in moderate-to-severe plaque psoriasis. FYB202 and the reference product Stelara were also well tolerated in Study FYB202-01-01 and Study FYB202-01-02 in healthy volunteers. There were no clinically remarkable differences in the incidence and nature of treatment-emergent adverse events (TEAEs). The overall evaluation of tolerability and safety confirmed the known safety profile for ustekinumab. Therefore, the same identified and potential risks of Stelara published in the Stelara risk management summary are applied for FYB202.

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

Not applicable. Biosimilarity of FYB202 to Stelara was demonstrated. The overall evaluation of tolerability and safety of FYB202 confirmed the known safety profile for ustekinumab.

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

Not applicable.

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

The safety concerns in this initial RMP submission for FYB202 are identical to the current safety concerns of Stelara (RMP version 27.3).

Important identified risks associated with the use of FYB202:

- None

Important potential risks associated with the use of FYB202:

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

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

Details on important identified/potential risks (potential mechanisms, evidence source(s) and strength of evidence, characterisation of the risk, risk factors and risk groups, preventability, impact on the risk-benefit balance of the product, and public health impact, references, all as applicable) are taken from the Stelara RMP version 27.3.

In the subsection 'characterisation of the risk', for the originator Stelara, proportion of subjects with relevant events will be presented as given in the Stelara RMP version 27.3. The percentage of subjects with one or more events associated with a specific important identified or potential risk is provided for the 'controlled portions population' (ustekinumab vs placebo/comparator) and the 'all clinical trials population' (ustekinumab vs placebo/comparator) across all clinical indications, psoriasis, PsA, CD and UC (all studies). The number of subjects evaluated in the placebo/comparator group was the same in the 'controlled portions populations' and the 'all clinical trials populations'. The number of subjects evaluated in the ustekinumab group is greater in the 'all clinical trials population' because in most trials placebo/comparator-treated subjects crossed over to receive ustekinumab. The average duration of follow-up was markedly longer in the 'all clinical trials population' than in the 'controlled portions population'. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated if the total number of events in the ustekinumab and placebo/comparator groups was >5.

For FYB202, data will be presented for patients with moderate-to severe plaque psoriasis (Study FYB202-03-01, N=392) and healthy volunteers (Study FYB202-01-01 and Study FYB202-01-02, pooled data, N=806). A total of 1198 subjects received ustekinumab in the FYB202 clinical development programme. Analyses for this RMP are attached as Annex 7.4.

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

Important Identified Risks: None

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

Potential mechanisms:

Studies performed in mice suggest that IL-12 may contribute to protective immune response to intracellular protozoa, bacteria and fungal pathogens (Trinchieri 2003), and IL-23 may contribute to immunity to *Klebsiella pneumoniae* (Happel et al 2005), *Mycobacterium tuberculosis* (Khader et al 2005), *Cryptococcus neoformans* (Kleinschek et al 2006) and *Candida albicans* (Acosta-Rodriguez et al 2007).

Humans who are genetically deficient for IL-12/23p40 or IL12 Rβ1 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 bacteria and common opportunistic protozoa. These individuals are susceptible to non-TB primary mycobacteria infection, including BCG and recurring *Salmonella sp.* (Fieschi and Casanova 2003; Novelli and Casanova 2004). Filipe-Santos et al (2006) reviewed inborn errors of IL-12/23 and reported that these patients, when vaccinated with BCG, developed BCG disease. They also found that these patients were more susceptible to salmonella infections.

Evidence source(s) and strength of evidence:

Published non-clinical and medical literature suggest that inhibition of IL-12/23 may predispose patients to serious infection. 'Serious infections (including mycobacterial and salmonella infections)' are considered an important potential risk with FYB202 based upon the theoretical risk identified from non-clinical data and in humans who are genetically deficient for the cytokines that are inhibited by FYB202 (IL-12/23p40 or IL12 Rβ1). However, the risk of developing serious infections (including mycobacterial and salmonella infections) in subjects on anti-IL-12/23p40 therapy such as FYB202 is currently unknown.

Across clinical trials in all indications for which FYB202 is approved, analysis for serious infections in pooled data of the originator Stelara during the controlled period does not suggest an increased risk of serious infections in the overall ustekinumab-treated population.

Characterisation of the risk:

Originator: In adult patients of the 'all clinical trials population' of Stelara studies (N=7253, average duration of follow-up 114.1 weeks), serious infections occurred in 3.9% ustekinumab-treated vs 1.2% placebo/comparator-treated subjects; (source: Table SVII.1, Stelara RMP Version 27.3). Three (<0.1%) patients died, 269 (3.7%) patients recovered, and 10 (0.1%) patients did not recover. In 9 (0.1%) patients, infection was mild, in 121 (1.7%) moderate and in 152 (2.1%) severe. In the 'controlled portions population' (N=5095, average duration of follow-up 11.5 weeks), serious infections occurred in 0.6% of ustekinumab-treated vs 0.6% placebo/comparator-treated subjects, OR 1.011 (95% CI 0.562, 1.818).

In adult patients of the 'all clinical trials population' of Stelara studies (N=7407, average duration of follow-up 113.1 weeks), mycobacterial and salmonella infections occurred in 0.1% ustekinumab-treated vs. 0.0% placebo/comparator-treated subjects (source: Table SVII.2, Stelara RMP Version 27.3); in 1 (<0.1%) subject infection was serious; 5 (0.1%) patients recovered; in 1 (<0.1%) subject infection was mild; in 3 (<0.1%) subjects infections were moderate and in 1 (<0.1%) subject infection was severe. In the 'controlled portions population' (N=5221, average duration of follow-up 11.5 weeks), such infections did not occur.

In paediatric patients of the 'all clinical trials population' of Stelara studies (N=154, average duration of follow-up 68.5 weeks) serious infections occurred in 1.9% (n=3) ustekinumab-treated vs 0.0% placebo/comparator-treated subjects (source: Table SVII.3, Stelara RMP Version 27.3); infections were moderate in severity and all patients recovered. In the 'controlled portions population' (N=73, average duration of follow-up 12.3 weeks), such infections did not occur.

Biosimilar: TEAEs in the integrated clinical database of Study FYB202-03-01 and the pooled data of Study FYB202-01 and Study FYB202-01-02 were searched in the MedDRA system organ class (SOC) Infections and infestations (MedDRA v24.0 for psoriasis patients and MedDRA version 25.1 for healthy volunteers; Annex 7.4, Listing 1.2.2.1, Listing 2.2.2.1). Results are shown in the following tables. All patients (4) with serious infections recovered, none was assessed as related to study intervention by the Investigator. No serious infections were reported in healthy volunteers. No mycobacterial or salmonella infections were reported.

Table SVII. 1: Serious infections (including mycobacterial and salmonella infections), patients with moderate-to-severe plaque psoriasis before re-randomisation; SAF

Adverse events	**FYB202 (N=197) n (%)**	**Stelara EU (N=195) n (%)**
Serious TEAEs	1 (0.5%)[a]	0
At least possibly IMP-related serious TEAEs	0	0
Worst severity	NA	NA
Worst outcome	NA	NA

SOC Infections and infestations
[a] MedDRA PT: Covid-19 pneumonia (moderate)
IMP =investigational medicinal product, NA = not applicable

Source: Annex 7.4, Listing 2.2.2.1

Table SVII.2: Serious infections (including mycobacterial and salmonella infections), patients with moderate-to-severe plaque psoriasis after re-randomisation; RRAS

Adverse events	**FYB202-FYB202 (N=189) n (%)**	**Stelara EU-Stelara EU (N=97) n (%)**	**Stelara EU-FYB202 EU (N=89) n (%)**
Serious TEAEs	3 (1.6%)[a]	0	0
At least possibly IMP-related serious TEAEs	0	0	0
Worst severity	NA	NA	NA
Worst outcome	NA	NA	NA

SOC Infections and infestations
[a] MedDRA PTs: Covid-19 (2; 1 severe, 1 moderate), Appendicitis perforated (1; severe)
NA = not applicable

Source: Annex 7.4, Listing 2.2.2.1

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 FYB202 or will have to choose a medication other than FYB202. Patients with active infection will have to choose an alternative medication and discontinue use of FYB202 until the infection is cleared. Patients who develop infections may potentially have a more severe course due to the use of an immunomodulatory agent such as ustekinumab. This important potential risk needs to be carefully weighed against the benefit conferred by use of ustekinumab.

Risk factors and risk groups:

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

TB: The most common risk factors for the development of TB include conditions impairing the development of effective cell-mediated immunity to the infection (ie, advanced age, human immunodeficiency virus [HIV] infection), alcohol abuse, malignancy, corticosteroids or other immunosuppression, connective tissue disease, renal failure, 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 high TB burden (incidence >300 TB cases/100,000 population/year) or have travelled to these locations may be at higher risk. Exposure in the health care setting or in high-density institutions (ie, prisons) may also put patients at higher risk of development of TB. The possibility of latent TB must be considered, especially in patients who have immigrated from or travelled to countries with a high prevalence of TB or had close contact with a person with active TB. In patients who are severely ill or immunocompromised, tuberculin tests yield false negative results.

Non-TB mycobacterial (NTM) infections: A retrospective review performed in Australia, found that significant risk for non-HIV-associated pulmonary *Mycobacterium avium/Mycobacterium intracellulare* complex (MAC) disease included male sex (OR=2.1; 95% CI: 1.0-4.5) and age ≥50 years (OR=26.5; 95% CI: 10.9-67.3; O'Brien et al 2000). Similarly, in a US study (Cassidy et al 2009) including 933 patients with 1 or more NTM isolates, pulmonary disease prevalence was highest in persons aged >50 years (15.5 cases per 100,000 persons). In addition, chronic respiratory disease, especially chronic obstructive pulmonary disease treated with inhaled corticosteroids therapy is a strong risk factor for NTM pulmonary disease (Andrejak et al 2013). Prolonged occupational exposure to soil was an important risk factor for MAC infection in a US study (Reed et al 2006).

Salmonella: Factors that could increase risk of salmonella infection include activities that result in close contact with salmonella (eg, international travel, owning a pet bird or reptile) and health issues that weaken the resistance to infection (eg, stomach or bowel disorders leading to use of antacids, recent antibiotic use, inflammatory bowel disease [IBD], or impaired immunity from acquired immune deficiency syndrome, sickle cell disease, malaria, anti-rejection drugs after organ transplants and corticosteroids) (Mayo Clinic 2022).

Preventability:

FYB202 is contraindicated in patients with a clinically important, active infection (eg, active TB (SmPC section 4.3 [Contraindications]). To prevent serious infections, it is recommended that live vaccines are not given concomitantly with FYB202 (SmPC section 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 recommend for 6 months following birth or until ustekinumab infant serum levels are undetectable (SmPC section 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 FYB202 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 FYB202 should not be administered until the infection resolves.

TB: FYB202 must not be given to patients with active TB. FYB202 should not be given to patients with latent TB unless treatment for latent TB is initiated prior to administering FYB202, including those patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving FYB202 should be monitored closely for signs and symptoms of active TB during and after treatment.

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

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

Impact on the risk-benefit balance of the product:

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

Further characterisation of the risk is conducted through routine pharmacovigilance activities.

Public health impact:

The potential public health impact is not known.

Important Potential Risk: Malignancy

Potential mechanisms:

Scientific literature suggests that IL-12 can contribute to tumour immunosurveillance (Colombo and Trinchieri 2002) and exogenous IL-12 can promote tumour-directed cytotoxic T cell responses in tumour vaccine strategies. In contrast, IL-23 has been reported to promote tumour growth in animal models. The preponderance of evidence from the published literature (knockout models where IL-23 is ablated) suggests that the risk for a malignancy may actually be reduced in the setting of IL-23 inhibition. However, conflicting data from a limited number of studies in mouse models and from photocarcinogenicity experiments point to an increased risk of malignancy in IL-23p19-deficient mice exposed to ultraviolet B radiation. Studies in mice genetically deficient in IL-12, or mice treated with high doses of an anti-mouse IL-12/23p40 antibody, suggest that IL-12 contributes to immunity against certain mouse models of neoplasia (Rao et al 1997). Cárdenes et al (2010) described a 25-year-old patient with IL-12Rβ1 deficiency who developed oesophageal carcinoma. However, the contribution of endogenous human IL-12 or Il-23 to tumour immunosurveillance remains unclear.

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 Stelara clinical trials across indications, the rate of malignancy other than non-melanoma skin cancer (NMSC) was low and was balanced between the ustekinumab and comparator groups.

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

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

Characterisation of the risk:

Originator: In the 'all clinical trials population' of Stelara studies (N=7407, average duration of follow-up 113.1 weeks), non-melanoma skin cancer (NMSC) occurred in 1.0% ustekinumab-treated vs 0.1% placebo/comparator-treated subjects (source: Table SVII.4, Stelara RMP Version 27.3). In 4 patients (0.1%) NMSC was serious. No patient died, 63 (0.9%) patients recovered, and 8 (0.1%) patients did not recover. In 36 (0.5%) patients NMSC was mild, in 33 (0.4%) moderate and in 2 (<0.1%) severe. In the 'controlled portions population' of Stelara studies (N=5221, average duration of follow-up 11.5 weeks), NMSC occurred in 0.1% ustekinumab-treated vs 0.1% placebo/comparator-treated subjects, OR 1.801 (95%CI 0.374, 8.675).

In the 'all clinical trials population' of Stelara studies (N=7407, average duration of follow-up 113.1 weeks), malignancies other than NMSC occurred in 1.1% ustekinumab-treated vs. 0.1% placebo-treated subjects (source: Table SVII.5, Stelara RMP Version 27.3); 67 (0.9%) of these malignancies were serious; 4 (0.1%) patients died, 39 (0.5%) patients recovered, 35 (0.5%) patients did not recover; 13 (0.2%) of these malignancies were mild, 23 (0.3%) were moderate and 42 (0.6%) were severe. In the 'controlled portions population' (N=5221, average duration of follow-up 11.5 weeks),

malignancies other than NMSC occurred in 0.1% ustekinumab-treated vs <0.1% placebo/comparator-treated subjects.

Biosimilar: TEAEs in the integrated clinical database of Study FYB202-03-01 and the pooled data of Study FYB202-01 and Study FYB202-01-02 were searched with the SMQ Malignancies (narrow) (MedDRA v24.0 for psoriasis patients and MedDRA version 25.1 for healthy volunteers; Annex 7.4, Listing 1.2.2.2, Listing 2.2.2.2). In Study FYB202-01-01, serious, severe 'glioblastoma' (PT Glioblastoma) was diagnosed in a 39-year-old female patient, 97 days after the SC injection of 45 mg ustekinumab as Stelara EU. The patient died. The Investigator assessed the relationship to study intervention as unlikely. In Study FYB202-03-01, serious, moderate 'right kidney tumor with lymph node metastases' (PT Renal cancer metastatic) was diagnosed, 149 days after the 1st SC injection (Week 0) of 45 mg ustekinumab as Stelara EU (the patient had also received ustekinumab injections at Week 4 and Week 16). The patient did not recover. The Investigator assessed the relationship to study intervention as unlikely. In Study FYB202-01-02, no malignancy occurred.

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving the originator Stelara or FYB202. Thus, caution should be exercised when considering the use of FYB202 in these patients (SmPC section 4.4 [Special Warnings and Precautions of Use]).

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

Risk factors and risk groups:

Among psoriasis patients, increased risk of solid cancers appears to be related to alcohol drinking and cigarette smoking. In addition, exposure to PUVA and immunosuppressants, including cyclosporin and possibly MTX, has been associated with squamous cell carcinoma in psoriasis patients (Pouplard et al 2013). General risk factors for malignancy include increasing age, life-style 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 malignancy in patients with IBD include but are not limited to smoking, ongoing inflammation and carcinogenic effects of immunosuppressive drugs.

Preventability:

Predictability and preventability of the development of malignancy is not known. Protection from UV exposure, either solar or from tanning beds may decrease the risk of an individual developing a cutaneous malignancy. As indicated in the SmPC section 4.4 (Special Warnings and Precautions for Use), caution should be exercised when considering the use of FYB202 in patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

All patients, in particular those older 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 NMSC (SmPC section 4.4 [Special Warnings and Precautions for Use]).

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

Impact on the risk-benefit balance of the product:

Although malignancies have been reported in patients treated with ustekinumab in clinical trials and in the post-marketing setting, 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 risk is conducted through routine pharmacovigilance activities.

Public health impact:

The potential public health impact is not known.

Important Potential Risk: Cardiovascular Events

Potential mechanisms:

Patients with severe psoriasis are more likely to demonstrate cardiovascular (CV) risk factors such as obesity, diabetes and hypertension when compared with those with no or mild psoriasis (Neimann et al 2006). The presence of systemic inflammation in combination with metabolic abnormalities may act in a synergistic manner to increase cardiovascular risk in these patients (Masson et al 2020). The greatest risk of myocardial infarction (MI) is found in young patients with severe psoriasis (Gelfand et al 2006). As in psoriasis, patients with PsA are reported to be at increased risk for occlusive vascular diseases, including MI and stroke (Husted et al 2011, Tobin et al 2010, Li et al 2012, Gladman DD, Ang M, Su L, Tom BD, Schentag CT, Farewell VT. Cardiovascular morbidity in psoriatic arthritis. Ann Rheum Dis. 2009;68(7):1131-1135. doi:10.1136/ard.2008.094839

). The potential mechanistic link between psoriasis and CV events, if any, is unclear.

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

Evidence source(s) and strength of evidence:

The risk of developing CV events in subjects on anti-IL-12/23p40 therapy such as FYB202 is currently unknown.

A numeric imbalance in rates of investigator-reported major cardiovascular evens (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. According to additional analyses, the overall rates of MI 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. Through approximately 5 years of follow-up in CD clinical trial and approximately 4 years of follow-up in UC clinical trials, the incidence of serious MACE was low in ustekinumab-treated subjects, with no consistent evidence that ustekinumab increases CV risk. Across indications, analysis of MACE in controlled portions of the pooled clinical trial data does not currently suggest a significant increased risk of MACE in subjects treated with ustekinumab.

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 patients with psoriasis and PsA populations, CV events are considered an important potential risk for ustekinumab.

Characterisation of the risk:

Originator: Cardiovascular events were defined as serious major cardiovascular events (cardiovascular death, non-fatal MI, or non-fatal stroke) and were either independently adjudicated or were identified by internal clinical review by physicians. The clinical review includes clinical trial SAEs occurring in the SOCs of Cardiac disorders, Nervous system disorders, Investigations, Vascular disorders, and all cardiovascular deaths and deaths of unknown cause. In the 'all clinical trials population' of Stelara studies (N=7407, average duration of follow-up 113.1 weeks), cardiovascular events occurred in 0.8% ustekinumab-treated vs 0.1% placebo/comparator-treated subjects (source: Table SVII.6, Stelara RMP Version 27.3). The events were serious in 61 (0.8%) patients; 11 (0.1%) patients died, 46 (0.6%) patients recovered, and 4 (0.1%) patients did not recover; for 1 (<0.1%) patient seriousness/outcome is missing. In 3 (<0.1%) patients severity was mild, in 13 (0.2%) moderate and in 46 (0.6%) severe. In the 'controlled portions population' of Stelara studies (N=5221, average duration of follow-up 11.5 weeks), cardiovascular events occurred in 0.1% ustekinumab-treated vs 0.1% placebo/comparator-treated subjects, OR 1.286 (95% CI 0.249, 6.631).

Biosimilar: Serious TEAEs in the integrated clinical database of Study FYB202-03-01 and the pooled data of Study FYB202-01 and Study FYB202-01-02 were searched in the SOCs Cardiac disorders, Nervous system disorders, Investigations, and Vascular disorders (MedDRA v24.0 for psoriasis patients and MedDRA version 25.1 for healthy volunteers; Annex 7.4, Listing 1.2.2.3, Listing 2.2.2.3). In addition, all non-serious TEAEs in these SOCs were medically reviewed; no relevant cardiovascular events were retrieved. There were no serious cardiovascular events. There were no cardiovascular deaths and no deaths of unknown cause.

There is evidence for an increased background risk of CV disease in patients with psoriasis and IBD (Cainzos-Achirica et al 2020), 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 in adequate treatment of CV risk factors. The impact of MACE on the individual patient may be very significant. Events of MACE may result in fatal outcome.

Risk factors and risk groups:

Risk factors in the development of CV disease are well known and include hypertension, hypercholesterolaemia, diabetes, smoking, age, male sex, obesity, and family history. The PsA, psoriasis and IBD populations share certain risk factors such as increase CV risk, increased body weight, and increased BMI (Augustin et al 2010, Bostoen et al 2014, Román and Muñoz 2011, Kristensen et al 2013, Dregan et al 2014).

Preventability:

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

Impact on the risk-benefit balance of the product:

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

Public health impact:

The potential public health impact is not known.

Important Potential Risk: Serious Depression Including Suicidality

Potential mechanisms:

Depression is a complex disease with a variety of biological theories for the pathophysiology. The mechanism by which ustekinumab could cause depression is unknown.

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 ustekinumab (FYB202 SmPC section 4.8 [Undesirable Effects]) and PL section 4). The incidence of serious depression including suicidality across indications remains low.

The available safety data from clinical studies and post-marketing experience have not identified a safety signal of suicidal ideation or suicide attempt (including completed suicide). However, based on the severity of these events, serious depression including suicidality is considered an important potential risk for ustekinumab.

Characterisation of the risk:

Originator: In the 'all clinical trials population' of Stelara studies (N=7407, average duration of follow-up 113.1 weeks), serious depression (including suicidality) occurred in 0.3% ustekinumab-treated vs 0.1% placebo-treated subjects (source: Table SVII.7, Stelara RMP Version 27.3). The event was serious in 20 (0.3%) patients; 3 (<0.1%) patients died, 14 (0.2%) patients recovered, and 3 (<0.1%) patients did not recover. In 2 (<0.1%) patients severity was mild, in 7 (0.1%) moderate, and in 11 (0.1%) severe. In the 'controlled portions population' (N=5221, average duration of follow-up 11.5 weeks), serious depression (including suicidality) occurred in 0.1% ustekinumab-treated vs <0.1% placebo-treated subjects.

Biosimilar: TEAEs in the integrated clinical database of Study FYB202-03-01 and the pooled data of Study FYB202-01 and Study FY202-01-02 were searched with the SMQ Depression and suicide/self-injury (broad) (MedDRA v24.0 for psoriasis patients and MedDRA version 25.1 for healthy volunteers; Annex 7.4, Listing 1.2.2.4, Listing 2.2.2.4). No serious events were retrieved.

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 psychological impact and the possibility of death from suicide attempts.

Risk factors and risk groups:

Risk factors for depression include older age and associated neurological conditions; uncontrolled, poorly treated psoriasis; recent childbirth; stressful life events; a personal or family history of depression; and selected medical comorbid conditions including psoriatic conditions and IBD. Suicide rates are twice as high in families of suicide victims (Fancher and Kravitz 2007).

Preventability:

There is no known means of preventing depression.

Impact on the risk-benefit balance of the product:

Up to now, no significant impact on the risk-benefit balance of the product is evident.

Further characterisation of the risk factors is conducted through routine pharmacovigilance activities.

Public health impact:

The potential public health impact is not known.

Important Potential Risk: Venous Thromboembolism

Potential mechanisms:

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

However, patients with IBD are at higher risk of venous thrombosis. VTE in patients with IBD is a multifactorial event that involves both hereditary (factor V Leiden mutation, G20210A mutation in the prothrombin gene, and homozygous C677T mutation in the methylenetetrahydrofolate reductase gene) and acquired factors (dehydration, indwelling catheters, prolonged immobilisation, hyperhomocysteinaemia, surgical interventions, active disease with 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 contribute to a higher prothrombotic state. These mechanisms include:

- Increased plasma levels of recognised risk factors for thrombosis (e.g., TNFα, IL-6 and IL-8 levels, several of which are also considered to be acute phase reactants) and decreased levels of natural anticoagulants;
- Reduced fibrinolytic activity;
- Endothelial abnormalities that are mainly represented by the downregulation of the anticoagulant thrombomodulin and endothelial protein C receptor, which in turn affects the conversion of protein C into its activated form;
- Abnormalities of platelets, such as thrombocytosis and increased activation and aggregation (Papa et al 2014).

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 biological plausibility for the inhibition of IL-12/23 contributing to the development of thrombosis.

Evidence source(s) and strength of evidence:

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

Venous thromboembolism was originally identified as an important potential risk based on data collected through 44 weeks of treatment in the ustekinumab CD clinical trials. Through approximately 5 years of follow-up in CD clinical trials and approximately 4 years of follow-up in UC clinical trials, while there is a slight imbalance across treatment groups in the reporting of all vascular thrombotic events, the overall incidence per 100 subject-years of venous thromboembolism in CD and UC clinical

trials conducted with the originator, was 1% in ustekinumab-treated patients and is within the range of 1-8% reported in the IBD literature (Alkim et al 2017; Danese et al 2007; Nguyen et al 2014).

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

Characterisation of the risk:

Originator: In the 'all clinical trials population' of Stelara studies (N=7407, average duration of follow-up 113.1 weeks), venous thromboembolism occurred in 0.6% ustekinumab-treated vs 0.2% placebo-treated subjects (source: Table SVII.8, Stelara RMP Version 27.3). The event was serious in 18 (0.2%) patients; 1 (<0.1%) patient died, 34 (0.5%) patients recovered, and 7 (0.1%) patients did not recover. In 11 (0.1%) patients severity was mild, in 19 (0.3%) moderate, and in 12 (0.2%) severe. In the 'controlled portions population' (N=5221, average duration of follow-up 11.5 weeks), venous thromboembolism occurred in 0.1% ustekinumab-treated vs <0.1% placebo-treated subjects, OR 3.086 (0.372, 25.629).

Biosimilar: TEAEs in the integrated clinical database of Study FYB202-03-01 and the pooled data of Study FYB202-01 and Study FYB202-01-02 were searched with the SMQ Embolic and thrombotic events, venous (broad) (MedDRA v24.0 for psoriasis patients and MedDRA version 25.1 for healthy volunteers; Annex 7.4, Listing 1.2.2.6, Listing 2.2.2.6). In Study FYB202-03-01, 2 patient experienced Pulmonary embolism. In one patient, the serious event started 17 days after the 1st SC injection of 45 mg ustekinumab as FYB202. The event was moderate in severity and the patient recovered. In another patient, the non-serious event, together with serious and severe Respiratory failure, started 350 days after the 1st SC injection of 45 mg ustekinumab as Stelara EU. The event was severe in severity and the patient recovered. The Investigator assessed the relationship of both events as unlikely related to the study intervention. No events of VTE occurred in healthy volunteers.

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. IBD patients have about a 3-fold higher risk of VTE compared with the general population, with the absolute risk being much higher in the hospital setting compared with the nonhospital setting (Nguyen et al 2014). Patients with IBD require vigilance in adequate treatment of VTE risk factors.

Risk factors and risk groups:

Patients suffering from IBD, namely CD or UC, are more prone to thromboembolic complications compared with the general population (Zezos et al 2014).

A study of IBD patients conducted in the UK reported that there was an increased risk of VTE during disease flares and chronic activity (Grainge et al 2010). In a Danish population study that included children and adults, the highest risk of VTE was in the 0-20 years group with an HR of 6.6 (95% CI: 3.3-13.2) compared with 1.6 (95% CI: 1.5-1.8) for the ≥60 years age group (Kappelman et al 2011). The risk has also been reported to be greater for males (incidence rate of 1.34 per 1000 patient-years) than for females (incidence rate of 0.73 per 1000 patient-years). Smoking and the need for steroid treatment have also been shown to be risk factors for VTE with ORs of 3.46 (95% CI: 1.14-10.5) and 2.97 (95% CI: 0.99-8.92), respectively (Vegh et al 2015).

Preventability:

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

Impact on the risk-benefit balance of the product:

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

Further characterisation of the risk is conducted through routine pharmacovigilance activities.

Public health impact:

The potential public health impact is not known.

Important Potential Risk: Exposure During Pregnancy

Potential mechanisms:

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

The effects of exposure to FYB202 on the developing fetus are not known.

Evidence source(s) and strength of evidence:

The effects of ustekinumab during pregnancy are not known.

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

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

Characterisation of the risk:

Originator: A total of 3648 medically confirmed and medically unconfirmed ustekinumab cases with maternal exposure were identified from clinical trials and the post-marketing setting until 31 December 2021 (source: Table SVII.9, Stelara RMP Version 27.3). The following outcomes were reported (single cases with more than one pregnancy outcome): 1084 live births, thereof 52 with congenital anomalies/birth defects, 65 with other AEs, 906 with no AE or congenital anomaly/birth defect, and 61 premature births; 270 spontaneous abortions, 84 elective abortions, 10 unspecified abortions, 2 missed abortions, 12 ectopic pregnancies, 12 intrauterine death/foetal demise/neonatal demise/still birth, and 2218 pregnancies continuing or for which no outcome was reported. A total of 604 medically confirmed and medically unconfirmed ustekinumab cases with paternal exposure were identified from clinical trials and the post-marketing setting until 31 December 2021 (source: Table SVII.10, Stelara

RMP Version 27.3). The following outcomes were reported (single cases with more than one pregnancy outcome):297 live births, thereof 10 with congenital anomalies/birth defects, 18 with other AEs, 249 with no AE or congenital anomaly/birth defect, and 20 premature births; 7 elective abortions, 20 spontaneous abortions, 2 intrauterine death/foetal demise/neonatal demise/still birth, and 289 pregnancies continuing or for which no outcome was reported.

Biosimilar: TEAEs in the clinical database of Study FYB202-03-01 and the pooled data of Study FYB202-01 and Study FYB202-01-02 were searched for exposure during pregnancy with the high level term (HLT) Exposures associated with pregnancy, delivery, and lactation and the SMQ Congenital, familial and genetic disorders (MedDRA v24.0 for psoriasis patients and MedDRA version 25.1 for healthy volunteers; Annex 7.4, Listing 1.2.2.7, Listing 2.2.2.7). One pregnancy occurred in Study FYB202-03-01 with a congenital anomaly/birth defect. At 26 weeks gestational age, 55 days after the 5th injection of 45 mg ustekinumab as FYB202 (1st, 2nd and 3rd injection as Stelara EU, 4th injection as FYB202), the patient gave birth to 2 live female infants via Caesarean section. 46 days later, both infants were self-breathing, no gene defects identified, and no other findings except cranial malformation were noted in both children. One child had absence of left leg V digit and additional digit on right leg. No further follow-up information is available. The Investigator assessed the congenital anomaly as unlikely related to the study intervention (FYB202-03-01 CSR, Section 14.5.3).
Three pregnancies occurred in Study FYB202-01-02. Two of these pregnancies were terminated by elective abortion (no congenital anomalies reported), one of these pregnancies was also reported as SAE because pharmacological abortion with mifepristone resulted in Abortion incomplete, followed by uterine curettage. The 3rd pregnancy was detected at the end-of-study examination and followed up until delivery. A healthy child was born in June 2023 (FYB202-01-02 CSR, Section 12.3.2.2).

The effects of ustekinumab during pregnancy are not known. Toxicology studies indicate that ustekinumab crossed the placenta, however; non-clinical studies have shown no negative effect on the pregnant females or any foetal abnormalities.

Risk factors and risk groups:

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

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

Preventability:

As a precautionary measure, it is preferable to avoid the use of ustekinumab in pregnancy. Women of childbearing potential should use effective contraception during treatment and up to 15 weeks after treatment (FYB202 SmPC section 4.6 [Fertility, Pregnancy and Lactation]). FYB202 should be given to a pregnant woman only if the benefit clearly outweighs the risk.

Impact on the risk-benefit balance of the product:

The impact of drug exposure during pregnancy on the patient and the foetus is unknown and thus the impact of this risk on the risk-benefit balance of FYB202 is unclear.

Public health impact:

The potential public health impact is not known.

SVII.3.2. Presentation of the missing information

Missing information: Long-term safety in paediatric patients 6 years and older
Evidence source: Two clinical trials investigated the use of Stelara in paediatric psoriasis patients 6 years and older through 60 and 176 weeks, respectively.
Population in need of further characterisation: Paediatric patients with psoriasis ≥ 6 years of age with long-term exposure to ustekinumab.

Missing information: Long-term impact on growth and development in paediatric patients 6 years and older
Evidence source: Two clinical trials investigated the use of Stelara in paediatric psoriasis patients 6 years and older through 60 and 176 weeks, respectively.
Population in need of further characterisation: Paediatric patients with psoriasis ≥ 6 years of age with long-term exposure to ustekinumab.

Missing information: Long-term safety in adult patients with moderately to severely active Crohn's disease
Evidence source: Three Phase 3 trials investigated the use of Stelara in adult CD from the first dose of ustekinumab through maintenance Week 272.
Population in need of further characterisation: Adults with moderately to severely active CD who have been treated with ustekinumab beyond maintenance Week 272.

Missing information: Long-term safety in adult patients with moderately to severely active ulcerative colitis
Evidence source: One Phase 3 trial investigated the use of Stelara in adult UC from the first dose of ustekinumab through maintenance Week 220.
Population in need of further characterisation: Adults with moderately to severely active UC who have been treated with ustekinumab beyond maintenance Week 220.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

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

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns:

In line with the routine pharmacovigilance activities of the originator, specific questionnaires are provided in Annex 4 of this RMP for the following safety concerns:

Safety Concern	**Purpose/Description**
Serious infections (including mycobacterial and salmonella infections)	Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Serious Infections and Opportunistic Infections to collect information on serious infections and opportunistic infections and Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Tuberculosis to collect information on tuberculosis
Malignancy	Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Malignancies

	(including Lymphoma, Second and Secondary Malignancies) to collect information on malignancies (including lymphoma, second and secondary malignancies)
Cardiovascular events	Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Cardiovascular Events to collect information on cardiovascular events
Venous thromboembolism	Topic of Interest Questionnaire (TOIQ) for Venous Thromboembolism to collect information on venous thromboembolism

Other forms of routine pharmacovigilance activities: Follow-up of case reports: The minimum desired case information for biosimilar medicinal product includes the brand name and batch number of the suspect product. Additional efforts must be made to collect this information in accordance with GVP VI.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are planned.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are planned.

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

V.1. Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Serious infections (including mycobacterial and salmonella infections)	**Routine risk communication:** SmPC section 4.3 (Contraindications), 4.4 (Special Warnings and Precautions for Use), 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction), 4.6 (Fertility, Pregnancy and Lactation), and 4.8 (Undesirable Effects) PL section 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.4 (Special Warnings and Precautions for Use) • Guidance regarding evaluation of patients for TB infection, treatment of latent TB and administration of anti-TB therapy in patients with a history of latent or active TB prior to initiation of Fymskina. • Recommendation to monitor patients for signs and symptoms of active TB during and after Fymskina treatment. • Guidance for managing patients who develop a serious infection. • Recommendations regarding the administration of live vaccines to patients receiving ustekinumab and to infants exposed to ustekinumab in utero. (The same recommendations are included in SmPC section 4.5 [Interaction with Other Medicinal Products and other Forms of Interaction]). SmPC section 4.6 (Fertility, Pregnancy and Lactation) • Recommendation regarding the administration of live vaccines to infants exposed to ustekinumab in utero. PL section 2 • Guidance for patients who have recently had or are going to have a vaccination. • Guidance for mothers who received ustekinumab while pregnant and recommendation regarding the administration of live vaccines to infants exposed to ustekinumab in utero. • Guidance for patients who have had a recent infection, have any abnormal skin openings (fistulae), are over 65 years of age, or have recently been exposed to someone who might have TB.

	PL section 4 • Guidance for patients who develop signs of an infection or have open cuts or sores while using Fymskina. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription.
Malignancy	**Routine risk communication:** SmPC section 4.4 (Special Warnings and Precautions for Use) and 4.8 (Undesirable Effects) PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.4 (Special Warnings and Precautions for Use) • Guidance for monitoring patients for the appearance of non-melanoma skin cancer. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription.
Cardiovascular events	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription.
Serious depression including suicidality	**Routine risk communication:** SmPC section 4.8 (Undesirable Effects) PL section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription.

Venous thromboembolism	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription.
Exposure during pregnancy	**Routine risk communication:** SmPC section 4.6 (Fertility, Pregnancy, and Lactation) PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.6 (Fertility, Pregnancy and Lactation) • Recommendation for contraceptive use in women of childbearing potential and for at least 15 weeks after treatment. PL section 2 • Advice for patients who become pregnant, think they may be pregnant, or are planning to become pregnant while using Fymskina. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription.
Long-term safety in peadiatric 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 measures beyond the Product Information:** Legal status: Restricted medical prescription.
Long-term impact on growth and development in paediatric 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 measures beyond the Product Information: Legal status: Restricted medical prescription.
Long-term safety in adult patients with moderately to severely active Crohn's disease	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription.
Long-term safety in adult patients with moderately to severely active ulcerative colitis	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription.

V.2. Additional risk minimisation measures

None.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious infections (including mycobacterial and salmonella infections)	**Routine risk minimisation measures:** • SmPC 4.3 (Contraindications), 4.4 (Special Warnings and Precautions for Use), 4.5 (Interaction with Other Medicinal Products and Other Forms of Intervention), 4.6 (Fertility, Pregnancy and Lactation), and	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQs for serious infections and TB **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	4.8 (Undesirable Effects) • PL sections 2 and 4 **Additional risk minimisation measures:** None	
Malignancy	**Routine risk minimisation measures:** • SmPC section 4.4 (Special Warnings and Precautions for Use) and SmPC section 4.8 (Undesirable Effects) • PL section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQ Additional pharmacovigilance activities: None
Cardiovascular events	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQ **Additional pharmacovigilance activities:** None
Serious depression including suicidality	**Routine risk minimisation measures:** • SmPC section 4.8 (Undesirable Effects) • PL section 4 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Venous thromboembolism	**Routine risk minimisation measures:** None **Additional risk minimisation measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOIQ **Additional pharmacovigilance activities:**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	None	None
Exposure during pregnancy	**Routine risk minimisation measures:** • SmPC section 4.6 (Fertility, Pregnancy, and Lactation) • PL section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Long-term safety in paediatric psoriasis patients 6 years and older	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Long-term impact on growth and development in paediatric psoriasis patients 6 years and older	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Long-term safety in adult patients with moderately to severely active Crohn’s disease	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Long-term safety in adult patients with moderately to severely active ulcerative colitis	**Routine risk minimisation measures:** None **Additional risk minimisation measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	None	None

Part VI: Summary of the risk management plan

Summary of risk management plan for Fymskina (ustekinumab)

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

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

This summary of the RMP for Fymskina should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Fymskina's RMP.

I. The medicine and what it is used for

Fymskina is authorised for plaque psoriasis, psoriatic arthritis (PsA), paediatric plaque psoriasis, Crohn’s disease (CD), and ulcerative colitis (UC) (see SmPC for the full indication). It contains ustekinumab as the active substance and it is given by the intravenous (IV) or subcutaneous (SC) route of administration.

Further information about the evaluation of Fymskina’s benefits can be found in Fymskina’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage <link to the EPAR summary landing page>.

The link to the EPAR summary will be provided to the applicant as part of the cover letter in the CHMP opinion package. MAHs should use the same link for updates related to post-authorisation procedures.

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

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

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

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

Together, these measures constitute routine risk minimisation measures.

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

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

II.A List of important risks and missing information

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

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

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 non-clinical and medical literature suggest that inhibition of IL-12/23 may predispose patients to serious infection. 'Serious infections (including mycobacterial and salmonella infections)' are considered an important potential risk with Fymskina based upon the theoretical risk identified from non-clinical data and in humans who are genetically deficient for the cytokines that are inhibited by Fymskina (IL-12/23p40 or IL12 Rβ1). However, the risk of developing serious infections (including mycobacterial and salmonella infections)

	in subjects on anti-IL-12/23p40 therapy such as Fymskina is currently unknown. Across clinical trials in all indications for which ustekinumab is approved, analysis for serious infections in pooled data of the originator Stelara during the controlled period does not suggest an increased risk of serious infections in the overall ustekinumab-treated population.
Risk factors and risk groups	*Serious infections:* Risk factors for the development of serious infections include diabetes and other comorbidities, as well as the concomitant use of steroids, anti-tumor necrosis factor (TNF)s, other immunosuppressants, or other biologics. *Tuberculosis (TB):* The most common risk factors for the development of TB include conditions impairing the development of effective cell-mediated immunity to the infection (ie, advanced age, human immunodeficiency virus [HIV] infection), alcohol abuse, malignancy, corticosteroids or other immunosuppression, connective tissue disease, renal failure, diabetes, and pregnancy. A risk factor for the development of TB is exposure to TB, and patients who were born or lived in countries considered by the World Health organisation to have high TB burden (incidence >300 TB cases/100,000 population/year) or have travelled to these locations may be at higher risk. Exposure in the health care setting or in high-density institutions (ie, prisons) may also put patients at higher risk of development of TB. The possibility of latent TB must be considered, especially in patients who have immigrated from or travelled to countries with a high prevalence of TB or had close contact with a person with active TB. In patients who are severely ill or immunocompromised, tuberculin tests yield false negative results. *Non-TB mycobacterial (NTM) infections:* A retrospective review performed in Australia, found that significant risk for non-HIV-associated pulmonary *Mycobacterium avium/Mycobacterium intracellulare* complex (MAC) disease included male sex (odds ration [OR]=2.1; 95% confidence interval [CI]: 1.0-4.5) and age ≥50 years (OR=26.5; 95% CI: 10.9-67.3). Similarly, in a United States (US) study including 933 patients with one 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 corticosteroids 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 the resistance to infection (eg, stomach or bowel

	disorders leading to use of antacids, recent antibiotic use, inflammatory bowel disease [IBD], or impaired immunity from acquired immune deficiency syndrome, sickle cell disease, malaria, anti-rejection drugs taken after organ transplants and corticosteroids).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3 (Contraindications), 4.4 (Special Warnings and Precautions for Use), 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction), 4.6 (Fertility, Pregnancy and Lactation), and 4.8 (Undesirable Effects) PL sections 2 and 4 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. Because malignancies tend to take a long time to develop, long-term follow up is most relevant. In psoriasis patients treated for up to 5 years with continuous ustekinumab therapy, the risk of malignancies other than NMSC was not increased compared to the general US population. There was no evidence of an increased risk of malignancy through approximately 5 years of follow-up in CD patients and approximately 4 years of follow-up in UC patients treated with ustekinumab. 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, this topic warrants continuous surveillance and malignancy is considered an important potential risk.
Risk factors and risk groups	Among psoriasis patients, increased risk of solid cancers appears to be related to alcohol drinking and cigarette smoking. In addition, exposure to psoralen ultraviolet A (PUVA) and immunosuppressants, including cyclosporin and possibly methotrexate (MTX), has been associated with squamous cell carcinoma in psoriasis patients. General risk factors for malignancy include increasing age, life-style 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 malignancy in patients with IBD include but are not limited to smoking, ongoing inflammation and carcinogenic effects of immunosuppressive drugs.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 (Special Warnings and Precautions for Use) and 4.8 (Undesirable Effects) PL section 2 Additional risk minimisation measures: 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 Fymskina is currently unknown. A numeric imbalance in rates of investigator-reported major cardiovascular evens (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. According to additional analyses, 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. Through approximately 5 years of follow-up in CD clinical trial and approximately 4 years of follow-up in UC clinical trials, the incidence of serious MACE was low in ustekinumab-treated subjects, with no consistent evidence that ustekinumab increases CV risk. Across indications, analysis of MACE in controlled portions of the pooled clinical trial data does not currently suggest a significant increased risk of MACE in subjects treated with ustekinumab. 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 patients with psoriasis and PsA populations, CV events are considered an important potential risk for ustekinumab.
Risk factors and risk groups	Risk factors in the development of CV disease are well known and include hypertension, hypercholesterolaemia, diabetes, smoking, age, male sex, obesity, and family history. The PsA, psoriasis and IBD populations share certain risk factors such as increase CV risk, increased body weight, and increased body mass index.

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 ustekinumab (Fymskina SmPC section 4.8 [Undesirable Effects]) and Package Leaflet section 4). The incidence of serious depression including suicidality across indications remains low. The available safety data from clinical studies and post-marketing experience have not identified a safety signal of suicidal ideation or suicide attempt (including completed suicide). However, based on the severity of these events, serious depression including suicidality is considered an important potential risk for ustekinumab.
Risk factors and risk groups	Risk factors for depression include older age and associated neurological conditions; uncontrolled, poorly treated psoriasis; recent childbirth; stressful life events; a personal or family history of depression; and selected medical comorbid conditions including psoriatic conditions and IBD. Suicide rates are twice as high in families of suicide victims.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8 (Undesirable Effects) and PL section 4 PL section 4 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.). Venous thromboembolism (VTE) was originally identified as an important potential risk based on data collected through 44 weeks of treatment in the ustekinumab CD clinical trials. Through approximately 5 years of follow-up in CD clinical trials and approximately 4 years of follow-up in UC clinical trials, while there is a slight imbalance across treatment groups in the reporting of all vascular thrombotic events, the overall incidence per 100 subject-years of VTE in CD and UC clinical trials conducted with the originator, was 1% in ustekinumab-treated patients in both the CD and UC populations and is within the range of 1-8% reported in the IBD literature. Overall, safety results from the CD clinical trials through Week 272, UC clinical trials through Week 220, and clinical trials conducted for other indications, as well as cumulative post-marketing data, do not indicate

	an increased rate with ustekinumab treatment.
Risk factors and risk groups	Patients suffering from IBD, namely CD or 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 an increased risk of VTE during disease flares and chronic activity. In a Danish population study that included children and adults, the highest risk of VTE was in the 0-20 years group with a hazard ratio of 6.6 (95% CI: 3.3-13.2) compared with 1.6 (95% CI: 1.5-1.8) for the ≥60 years age group. The risk has also been reported to be greater for males (incidence rate of 1.34 per 1000 patient-years) than for females (incidence rate of 0.73 per 1000 patient-years). Smoking and the need for steroid treatment have also been shown to be risk factors for VTE with odds ratios of 3.46 (95% CI: 1.14-10,5) and 2.97 (95% CI: 0.99-8.92), respectively.

Important potential risk: Exposure during pregnancy	
Evidence for linking the risk to the medicine	The effects of ustekinumab during pregnancy are not known. Toxicokinetic analyses have confirmed that ustekinumab can cross the placenta; however, non-clinical studies have shown no adverse effect. Cumulative data do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (SmPC section 4.6 [Fertility, Pregnancy and Lactation]), but cases of exposure during pregnancy are still limited. 'Exposure during pregnancy' is considered an important potential risk because of the limitations of non-clinical investigations on this topic and the limited data in humans related to exposure during pregnancy.
Risk factors and risk groups	Patients who do not follow guidance on use of contraception or use contraception incorrectly are at risk of pregnancy. Most of the systemic antipsoriatic therapies are associated with significant toxic effects to the foetus and are recommended to be avoided during pregnancy. A recent update on the safety of IBD medications in pregnancy summarised that the available data provide reassuring information for providers caring for women with IBD and of childbearing age, although long-term effects of IBD medications on offspring need to be examined.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 (Fertility, Pregnancy, and Lactation) PL section 2 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 Fymskina.

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

There are no ongoing or planned additional pharmacovigilance activities for Fymskina.

Part VII: Annexes

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Annex 4 – Specific adverse drug reaction follow-up forms

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

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

Note: The above questionnaires are utilised in conjunction with standard case follow-up procedures to obtain complete case information which includes ustekinumab's brand name and batch number.

Follow-up forms (Versions 1.0)

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

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

Drug generic (TRADENAME):

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):

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

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

Drug generic (TRADENAME):

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

☐ Weight loss ≥10% of ideal body weight ☐ Head/Neck carcinoma ☐ Silicosis

☐ Diabetes ☐ Leukaemia/Lymphoma ☐ Positive HIV test

☐ Gastrectomy or jejunoileal bypass ☐ Household contact/Exposure to TB

☐ Organ/tissue transplant ☐ Prior/prolonged steroid use

☐ Prior BCG vaccination ☐ IV drug abuse

☐ Recent travel to endemic area ☐ Prior/prolonged immunosuppressant use

☐ Resident/employee at high risk setting (e.g. correctional institute, homeless shelter, nursing home, refugee camp, etc.)

Details:

2. Diagnostics

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

☐ Intradermal skin test

☐ Multipuncture skin test

Number of units administered:

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

Date of PPD: [dd-MMM-yyyy]

2nd PPD results (if applicable): mm of induration

Date of 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:

Type of tuberculosis:

☐ Pulmonary

☐ Extrapulmonary; Location:

☐ Disseminated; Location:

☐ Multi-drug resistant TB

Other laboratory results

Laboratory test		**Test result**	**Date [dd-MMM-yyyy]**
AFB smear	Sputum		
	Other (specify)		
Culture	Sputum		
	Other (specify)		
PCR MTb			
Quantiferon TB Gold			

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

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

Drug generic (TRADENAME):

1. **Relevant medical/family history** (provide prior diagnoses and details for checked items below)

☐ Previous malignancy (provide specific diagnosis):

☐ Occupational/exposure history:

☐ Excessive sun exposure (describe):

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

☐ History of radiation

Dose of radiation:

Area treated:

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

Indication for radiation:

Any radiation induced changes?

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

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

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

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

☐ In first degree relatives:

☐ In more distant relatives:

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

Age at first exposure to any TNF blocker:

☐ Previous administration of other immunosuppressive medications, antineoplastic medications, or other drugs, which have a risk of 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]

☐ Cytogenic 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 (including 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:

☐ Hodgkins lymphoma

Histologic subtype:

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

If yes, test results: ☐ EBV positive ☐ EBV negative:

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

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

(Ref. http://ctep.cancer.gov/protocolDEvelopment/electronic_applications/docs/aeguidelines.pdf)

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

Screening test/preventive measure	**Date [dd-MMM-yyyy]**	**Results (including units and reference ranges where applicable)**

3. Treatment

What was the response to the first treatment for malignancy?

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

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

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

Drug generic (TRADENAME):

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 ischaemic evaluation], dates, etc., below.)

☐ Hypertension

☐ Hyperlipidaemia/Hypercholesterolaemia/Hypertriglyceridaemia

☐ Obesity

☐ Coronary artery disease

☐ Myocardial infarction

☐ Valvular heart disease

☐ History of percutaneous coronary intervention

☐ Coronary artery bypass graft

☐ Congenital heart disease

☐ Arrhythmias

☐ Cardiomyopathy

☐ Pericarditis

☐ Congestive heart failure

☐ Peripheral artery disease

☐ Diabetes mellitus

☐ Renal impairment

☐ Liver disease

☐ Headaches

☐ Head trauma

☐ Transient ischaemic attack

☐ Ischaemic cerebrovascular accident

☐ Haemorrhagic cerebrovascular accident

☐ Other (specify):

Relevant family history:

☐ Coronary disease

☐ Stroke

☐ Hyperlipidaemia/Hypercholesterolaemia/Hypertriglyceridaemia

☐ Myocardial infarction

☐ Diabetes mellitus

☐ Family history of long QT syndrome

☐ Other (specify):

3. Adverse event: patient's symptoms/signs (Check all that apply and provide details below.)

☐ Dizziness	☐ Exercise tolerance	☐ Chest discomfort
☐ Palpitations	☐ Dyspnoea	☐ Haemoptysis
☐ Oedema	☐ 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:

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

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

Drug generic (TRADENAME):

1. Adverse event description

Patient's clinical signs and symptoms

☐ Leg/calf oedema	☐ Pain in calf/leg	☐ Haemoptysis
☐ Dyspnoea	☐ Chest pain/discomfort	☐ Syncope
☐ Tachypnoea	☐ Tachycardia	☐ Cough
☐ Headache	☐ Blurred visions	☐ 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 traveling and or sitting for long periods of time (>4 hours) prior to the event?		
Is there a current history of smoking?	☐ No	☐ Yes, details:
Is there a prior history of smoking?	☐ No	☐ Yes, details:
Is there a history of cancer?	☐ No	☐ Yes, details:
Any past medical history of autoimmune disease (i.e. collagen-vascular disease, inflammatory bowel disease) or myeloproliferative disease?	☐ No	☐ Yes, details:
Does the subject have a history of 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 the 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:

☐ Dysfibrinogenaemia ☐ Antiphospholipid syndrome ☐ Factor V Leiden mutation

☐ Protein C or S deficiency ☐ Elevated factor VIII levels ☐ Anti-thrombin deficiency

☐ Hyperhomocysteinaemia ☐ Prothrombin gene mutation ☐ Blood-clotting disorder

☐ Thrombophilia

Acquired risk factors:

☐ Reduced mobility (paralysis, paresis, travel, etc.) ☐ Recent surgery

☐ Indwelling central venous catheters ☐ Recent trauma

☐ Recent discontinuation of anticoagulants (e.g. heparin, warfarin, DOACs)

☐ Hormone replacement therapy (HRT) ☐ Hormonal contraceptives

☐ Polycystic ovary syndrome (PCOS) ☐ Pregnancy

☐ Postpartum (up to 3 months after childbirth)

☐ Phlebitis ☐ Lupus

☐ Inflammatory bowel disease ☐ Myeloproliferative disorders

☐ Diabetes mellitus ☐ Hyperlipidaemia

☐ Hypertension ☐ Dehydration

☐ Other significant medical co-morbidities or risk factors for DVT, specify:

If yes to any of the above, provide details:

Provide Well’s score, if calculated:

3. **Relevant results of diagnostic tests including 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 (IgG and IgM) or beta-2 glycoproteins antibodies		
Antiphospholipid antibodies (IgG and IgM)		

Lupus anticoagulant		
Heparin antibodies		
ANA and ANCA		
IL6 levels		
ADAMTS13 activity assay		
Ceruloplasmin		
Direct Coombs test		
Complement C3, C4		
Methylenetetrahydrofolate reductase gene mutation		
Prothrombin gene mutation (G20210A)		
Occult blood in stool		
COVID-19 test		
Troponins		
Brain natriuretic peptide		
Arterial blood gases		
Chest X-ray		
Electrocardiography		
Echocardiography		
Duplex ultrasonography		
MRI scan		
CT scan		
Contrast venography		
Pulmonary angiography		
Ventilation-perfusion scanning		

Provide details of any additional diagnostic results:

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

Not applicable.