EU Risk Management Plan for Imraldi (Adalimumab)

RMP version to be assessed as part of this application:

RMP version number: 8.0

Data lock point for this RMP: Mar 12, 2025

Date of final sign off: Jun 12, 2025

Rationale for submitting an updated RMP: To update the additional pharmacovigilance plan (BIOBADASER, ARTIS) and final reports

Summary of significant changes in this RMP:

<Additional pharmacovigilance plan>

The status of study, end date and final report of two category 3 post-authorization safety studies (PASS), ARTIS and BIOBADASER, are updated from "planned" to "completed" throughout this RMP.

<Summary of the safety concerns>

The missing information “Patients with immune compromised conditions”, “Long-term safety information in the treatment of children with uveitis” are removed from the list of safety concerns to align with that of the reference product

The missing information “Episodic treatment in Ps, UC and JIA reclassified to Episodic treatment in UC is reclassified to align with that of the reference product.

Other RMP versions under evaluation: None

Details of the currently approved RMP:

Version number: 7.1

Approved with procedure: EMEA/H/C/004279/IB/0047

Date of approval: Apr 07, 2022

Qualified Person responsible for Pharmacovigilance (QPPV) oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic si gnature is available on file.

In the absence of QPPV, deputy QPPV's signature is provided below:

Name: Yana Luciano Corrieri

Signature: [redacted] Date: 17-Jun-2025

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LIST OF ABBREVIATIONS

6-MP	6-mercaptopurine
ACR	American College of Rheumatology
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
ALS	Amyotrophic lateral sclerosis
ARTIS	Antirheumatic Therapies In Sweden
AS	Ankylosing spondylitis
AZA	Azathioprine
BCC	Basal cell carcinoma
CD	Crohn's disease
CDC	Complement-dependent cytotoxicity
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRP	C-reactive protein
CVA	Cerebrovascular accident
DNA	Deoxyribonucleic acid
DP	Drug product
DS	Drug substance
dsDNA	Double stranded DNA
ECG	Electrocardiogram
EEA	European Economic Area
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOW	Every Other Week
EU	European Union
Fc	Fragment crystallisable
FRET	Fluorescence resonance energy transfer
GBS	Guillain-Barré syndrome
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus

HCP	Health care professional
HIV	Human immunodeficiency virus
HL	Hodgkin's lymphoma
HLA	Human leucocyte antigen
HLGT	High-level group term
HLT	High-level term
HS	Hidradenitis suppurativa
HSTCL	Hepatosplenic T-cell lymphoma
IBD	Inflammatory bowel disease
ILD	Interstitial lung disease
IP	Investigational product
JIA	Juvenile idiopathic arthritis
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MS	Multiple sclerosis
MTX	Methotrexate
NF-κB	Nuclear factor kappa B
NHL	Non-Hodgkin's lymphoma
NMSC	Non-melanoma skin cancer
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
ON	Optic neuritis
PD	Pharmacodynamic(s)
PFS	Pre-filled syringe
PFP	Pre-filled pen
PK	Pharmacokinetic(s)
PML	Progressive multifocal leukoencephalopathy
PsA	Psoriatic arthritis
PsO	Psoriasis
PSC	Primary sclerosing cholangitis
PT	Preferred term
PUVA	Psoralen combined with ultraviolet A
PV	Pharmacovigilance
PY	Patient-Year

QPPV	Qualified Person for Pharmacovigilance
RA	Rheumatoid arthritis
RMP	Risk management plan
RPLS	Reversible posterior leukoencephalopathy syndrome
SAE	Serious adverse event
SJS	Stevens-Johnson Syndrome
SLE	Systemic lupus erythematosus
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
SOC	System Organ Class
TB	Tuberculosis
Tg	Transgenic
Th	T helper cell
TNF-α	Tumour necrosis factor-alpha
UC	Ulcerative colitis
ULN	Upper limit of normal
UV	Ultraviolet
WHO	World Health Organization

PART I: PRODUCT(S) OVERVIEW

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Adalimumab
Pharmacotherapeutic group(s) (ATC Code)	L04AB04
Marketing Authorisation Holder	Samsung Bioepis NL B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Imraldi
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Not applicable
	Summary of mode of action: Imraldi® is a proposed biosimilar to Humira® (Adalimumab). Adalimumab is a recombinant human monoclonal antibody produced in Chinese Hamster Ovary cells. Adalimumab binds specifically to tumour necrosis factor-alpha (TNF-α) and neutralises the biological function of TNF-α by blocking its interaction with the p55 and p75 cell surface TNF-α receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF-α, including changes in the levels of adhesion molecules responsible for leukocyte migration.
	Important information about its composition: Adalimumab is a recombinant human monoclonal antibody produced in Chinese Hamster Ovary cells.
Hyperlink to the Product Information	Product Information
Indication(s) in the EEA	Current: Rheumatoid arthritis (RA) Polyarticular juvenile idiopathic arthritis Enthesitis-related arthritis Ankylosing spondylitis (AS) Axial spondyloarthritis without radiographic evidence of AS (nr-axSpA) Psoriatic arthritis (PsA) Psoriasis (PsO) Paediatric plaque PsO Hidradenitis suppurativa (HS) Crohn's disease (CD) Paediatric CD Ulcerative colitis (UC) Paediatric UC Uveitis Paediatric uveitis
	Proposed:

	N/A
Dosage in the EEA	Current: <u>Adults</u> *Rheumatoid arthritis* The recommended dose of Imraldi for adult patients with rheumatoid arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection. Methotrexate should be continued during treatment with Imraldi. Glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, or analgesics can be continued during treatment with Imraldi. In monotherapy, some patients who experience a decrease in their response to Imraldi 40 mg every other week dosing may benefit from an increase in dosage to 40 mg adalimumab every week or 80 mg every other week. Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be reconsidered in a patient not responding within this time period. *Ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS and psoriatic arthritis* The recommended dose of Imraldi for patients with ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS and for patients with psoriatic arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection. Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be reconsidered in a patient not responding within this time period. *Psoriasis* The recommended dose of Imraldi for adult patients is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week starting one week after the initial dose. Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period. Beyond 16 weeks, patients with inadequate response to Imraldi 40 mg every other week may benefit from an increase in dosage to 40 mg every week or 80 mg every other week. The benefits and risks of continued 40 mg weekly or 80 mg every other week therapy should be carefully reconsidered in a patient with an inadequate response after the increase in dosage. If adequate response is achieved with 40 mg every week or 80 mg every other week, the dosage may subsequently be reduced to 40 mg every other week. *Hidradenitis suppurativa* The recommended Imraldi dose regimen for adult patients with hidradenitis suppurativa (HS) is 160 mg initially at Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later at Day 15

	(given as two 40 mg injections in one day). Two weeks later (Day 29) continue with a dose of 40 mg every week or 80 mg every other week (given as two 40 mg injections in one day). Antibiotics may be continued during treatment with Imraldi if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with Imraldi. Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period. Should treatment be interrupted, Imraldi 40 mg every week or 80 mg every other week may be re-introduced. The benefit and risk of continued long-term treatment should be periodically evaluated. *Crohn's disease* The recommended Imraldi induction dose regimen for adult patients with moderately to severely active Crohn's disease is 80 mg at week 0 followed by 40 mg at week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at week 0 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), 80 mg at week 2 (given as two 40 mg injections in one day), can be used with the awareness that the risk for adverse events is higher during induction. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Alternatively, if a patient has stopped Imraldi and signs and symptoms of disease recur, Imraldi may be re-administered. There is little experience from re-administration after more than 8 weeks since the previous dose. During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines. Some patients who experience decrease in their response to Imraldi 40 mg every other week may benefit from an increase in dosage to 40 mg Imraldi every week or 80 mg every other week. Some patients who have not responded by week 4 may benefit from continued maintenance therapy through week 12. Continued therapy should be carefully reconsidered in a patient not responding within this time period. *Ulcerative colitis* The recommended Imraldi induction dose regimen for adult patients with moderate to severe ulcerative colitis is 160 mg at week 0 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days) and 80 mg at week 2 (given as two 40 mg injections in one day). After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines. Some patients who experience decrease in their response to Imraldi 40 mg every other week may benefit from an increase in dosage to 40 mg Imraldi every week or 80 mg every other week.

Available data suggest that the clinical response is usually achieved within 2-8 weeks of treatment. Imraldi therapy should not be continued in patients failing to respond within this time period.

Uveitis

The recommended dose of Imraldi for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. There is limited experience in the initiation of treatment with Imraldi alone. Treatment with Imraldi can be initiated in combination with corticosteroids and/or with other non-biologic immunomodulatory agents. Concomitant corticosteroids may be tapered in accordance with clinical practice starting two weeks after initiating treatment with Imraldi.

It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis.

Paediatrics

Juvenile Idiopathic Arthritis (JIA)

The recommended dose of Imraldi for patients with polyarticular juvenile idiopathic arthritis from 2 years of age is based on body weight. Imraldi is administered every other week via subcutaneous injection.

Patient Weight	Dosing Regimen
10 kg to < 30 kg	20 mg every other week
≥ 30 kg	40 mg every other week

There is no relevant use of adalimumab in patients aged less than 2 years for this indication.

Enthesitis-related arthritis

The recommended dose of Imraldi for patients with enthesitis-related arthritis from 6 years of age is based on body weight. Imraldi is administered every other week via subcutaneous injection.

Patient Weight	Dosing Regimen
15 kg to < 30 kg	20 mg every other week
≥ 30 kg	40 mg every other week

Adalimumab has not been studied in patients with enthesitis-related arthritis aged less than 6 years.

Paediatric plaque psoriasis

The recommended Imraldi dose for patients with plaque psoriasis from 4 to 17 years of age is based on body weight.

Patient Weight	Dosing Regimen
15 kg to < 30 kg	Initial dose of 20 mg, followed by 20 mg given every other week starting one week after the initial dose
≥ 30 kg	Initial dose of 40 mg, followed by 40 mg given every other week

	starting one week after the initial dose

Adolescent hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)
The recommended Imraldi dose is 80 mg at week 0 followed by 40 mg every other week starting at week 1 via subcutaneous injection.

In adolescent patients with inadequate response to Imraldi 40 mg every other week, an increase in dosage to 40 mg every week or 80 mg every other week may be considered.

Paediatric Crohn's disease

The recommended dose of Imraldi for patients with Crohn's disease from 6 to 17 years of age is based on body weight.

Patient Weight	Induction Dose	Maintenance Dose Starting at Week 4
< 40 kg	- 40 mg at week 0, and 20 mg at week 2 In case there is a need for a more rapid response to therapy with the awareness that the risk for adverse events may be higher with use of the higher induction dose, the following dose may be used: - 80 mg at week 0 and 40 mg at week 2	20 mg every other week
≥ 40 kg	- 80 mg at week 0, and 40 mg at week 2 In case there is a need for a more rapid response to therapy with the awareness that the risk for adverse events may be higher with use of the higher induction dose, the following dose may be used: - 160 mg at week 0 and 80 mg at week 2	40 mg every other week

Patients who experienced insufficient response may benefit from an increase in dosage:
< 40 kg: 20 mg every week
≥ 40 kg: 40 mg every week

Paediatric ulcerative colitis

The recommended dose of Imraldi for patients from 6 to 17 years of age with ulcerative colitis is based on body weight.

Patient Weight	Induction Dose	Maintenance Dose Starting at Week 4*
< 40 kg	- 80 mg at week 0 (given as two 40 mg injections in one day) and - 40 mg at week 2 (given as one 40mg injection)	40 mg every other week
≥ 40 kg	- 160 mg at week 0 (given as four 40 mg injections in one day or two 40 mg injections per day for two consecutive	80 mg every other week

<table>
<tr><td></td><td>
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<tr><td></td><td>days) and
- 80 mg at week 2 (given as two 40mg injections in one day)</td><td></td></tr>
</table>
* Paediatric patients who turn 18 years of age while on Imraldi should continue their prescribed maintenance dose.

Continued therapy beyond 8 weeks should be carefully considered in patients not showing signs of response within this time period.

Paediatric uveitis

The recommended dose of Imraldi for paediatric patients with uveitis from 2 years of age is based on body weight.
<table>
<tr><th>Patient Weight</th><th>Dosing Regimen</th></tr>
<tr><td>< 30 kg</td><td>20 mg every other week in combination with methotrexate</td></tr>
<tr><td>≥ 30 kg</td><td>40 mg every other week in combination with methotrexate</td></tr>
</table>
</td></tr>
<tr><td></td><td>Proposed:
N/A</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>Current:

40 mg/0.8 ml solution for injection in pre-filled syringe
40 mg/0.8 ml solution for injection in pre-filled pen
40 mg/0.8 ml solution for injection in vial

40 mg/0.4 ml solution for injection in pre-filled syringe
40 mg/0.4 ml solution for injection in pre-filled pen</td></tr>
<tr><td></td><td>Proposed: N/A</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>No</td></tr>
</table>

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

This module is not required for a biosimilar in accordance with Good Pharmacovigilance Practices (GVP) Module V – Risk management systems Table V.5., Summary of minimum RMP requirements for initial marketing authorisation applications.[1]

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

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

Toxicity

The only non-clinical safety study was a 4-week repeated dose study of 32 mg/kg subcutaneous once weekly in cynomolgus monkeys, which evaluated the toxicological profiles of Imraldi® and US-sourced Humira®. As a result of this study, the toxicology profile of Imraldi and Humira were similar, as summarised below in Table SII.1.

Table SII.1: Summary of key safety findings from non-clinical studies and their relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Repeat dose toxicity: Imraldi, the reference drugs (US-sourced Humira), or a vehicle control was administered subcutaneously once weekly for 4 weeks to cynomolgus monkeys (3/sex) at dose levels of 0 or 32 mg/kg. In most animals, Imraldi and US-sourced Humira were well tolerated at a dose level of 32 mg/kg with no significant findings. There was no reference- or Imraldi effects on clinical observation, body weight, electrocardiogram (ECG), or clinical pathology parameters, and no ophthalmic findings attributed to test article administration which were consistent with the results of non-clinical studies of Humira performed by the originator. Furthermore, there were no macro- or microscopic findings or organ weight changes attributed to Imraldi or US-sourced Humira. There was no difference in terms of immunogenic parameters between Imraldi and US -sourced Humira. The result of immunotoxicity evaluation based on peripheral blood leukocyte analysis was similar between Imraldi and US-sourced Humira. The result of toxicokinetic analysis also indicated no significant differences in exposure to either Imraldi or US-sourced Humira.	Imraldi has been developed as a biosimilar to Humira. As no difference was observed in the repeated dose toxicity study, findings from the reference product can be referred. In the reference product's studies, the findings observed were driven by exaggerated pharmacology of adalimumab and it can be assumed that these findings are also relevant for humans.

Key safety findings (from non-clinical studies)	Relevance to human usage
Reproductive/Developmental toxicity: No reproductive studies were performed with Imraldi in line with the EU guidance on biosimilar products (CHMP guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005 Rev. 1)[2], which indicates that routine toxicological studies, such as reproduction toxicology, are not required.	Imraldi has been developed as a biosimilar to Humira. Consequently, the reproductive/developmental toxicity package developed for Humira should be considered when considering this type of toxicity.
Genotoxicity/Carcinogenicity: No genotoxicity/carcinogenicity studies were performed with Imraldi. Carcinogenicity studies were not conducted in line with the CHMP guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005 Rev. 1.[2]	Imraldi has been developed as a biosimilar to Humira. Consequently, the genotoxicity/carcinogenicity package developed for Humira should be considered when considering this type of toxicity.
Hepatotoxicity/Nephrotoxicity: No studies of hepatotoxicity or nephrotoxicity were performed with Imraldi.	According to the SmPC, Humira has not been studied in these patient populations; therefore, no dose recommendations can be made. [3]
Cardiotoxicity: No cardiotoxicity studies have been conducted in support of the safety profile of Imraldi.	No effects on the cardiovascular system have been noted in non-clinical studies for the reference product, Humira. Since Imraldi is being developed as a biosimilar, the safety profile of Humira can be considered with respect to cardiotoxicity.
Drug interactions: On the basis of the specificity of adalimumab and the extensive clinical experience with the reference product, no non-clinical studies pertinent to drug interaction were conducted.	According to the SmPC for Humira, no interaction studies have been performed with Humira. [3]

Safety pharmacology

Safety pharmacology studies were not performed in line with the CHMP guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical Issues; EMEA/CHMP/BMWP/42832/2005 Rev. 1.[2] Since Imraldi has been developed as a biosimilar to Humira, the safety pharmacology package developed for Humira should be considered when considering this type of toxicity.

In vitro studies were conducted at several functional levels including:

- Fab-associated functions (e.g. binding to target antigen: binding to soluble TNF-α (sTNF-α) and Fab-associated functions neutralisation of a soluble ligand, and apoptosis)
- Binding to relevant Fc (fragment crystallisable) gamma receptors (FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa [158V/V type]), to the neonatal Fc receptor (FcRn) and complement 1q (C1q), and

Fc-associated functions (e.g. antibody-dependent cellular cytotoxicity [ADCC]; complement-dependent cytotoxicity [CDC]).

- Additional biological properties: inflammatory bowel disease (IBD) associated assays (e.g. apoptosis assay in *in vitro* IBD model, inhibition of IL-8 cytokine release in an *in vitro* IBD model, evaluation of regulatory macrophage function), binding to transmembrane TNF-α (tmTNF-α) and LT- α3 (TNF- α), inhibitory activity on adhesion molecule (VCAM-1) expression, additional Fc-associated functions (e.g. FcγRIIIa binding assay [158F/F type] and FcγRIIIb binding assay), and antibody conformational array.

As the similarity range for the binding assays and cell based assays, the statistical analysis involved tolerance intervals of mean ±kSD (mean ±3SD for apoptosis assay, *in vitro* IBD model, inhibition of IL-8 cytokine release in *in vitro* IBD model, inhibition of sVCAM-1 adhesion molecule expression, transmembrane TNF-α binding assay, evaluation of regulatory macrophage induction function, FcγRIIIa binding assay [158F/F], FcγRIIIb binding assay, antibody confirmation array, and TNF-β [LTα3] binding assay) with two-sided tolerance limits of reference product batches. The overall results of the *in vitro* Fab-, and Fc-related biological assay and additional biological assay demonstrated similarity between Imraldi and EU Humira. The key findings from these studies are summarised in Table SII.2.

Table SII. 2:Summary of comparative in vitro non-clinical pharmacology studies

Study title	Key findings
TNF-α binding assay	Binding activity of Imraldi and the reference products to TNF-α was determined by fluorescence resonance energy transfer (FRET)-based competitive inhibition binding assay (FRET assay). The binding activity of Imraldi drug substance (DS) and drug product (DP) ranged from 90 to 105% relative to the bioassay standard. The binding activity of EU Humira ranged from 97 to 103%. TNF-α binding activities of all the Imraldi DS and DP were within the similarity range (84-115%). In conclusion, results indicate that TNF-α binding activities of Imraldi are highly similar to EU Humira.
TNF-α neutralisation assay by nuclear factor kappa B (NF-κB)reporter gene	Inhibitory activity of Imraldi and the reference products on the soluble TNF-α signalling pathway was measured through the TNF-α neutralisation assay using a 293-NF-κB Luc cell line. The potency of Imraldi DS and DP ranged from 93 to 105% relative to the bioassay standard and the potency of EU Humira ranged from 94 to 100%. Relative potencies of all the Imraldi DS and DP were within the similarity range (82-119%) which indicated that TNF-α neutralisation potencies of the Imraldi are highly similar to EU Humira.
Apoptosis assay	The apoptosis assay for Imraldi and the reference products was performed using Jurkat mTNF-α cells. The apoptosis activity of the Imraldi DS and DP ranged from 96 to 108% relative to the bioassay standard. The apoptosis activity of EU Humira ranged from 100 to 104%. Apoptosis activities of Imraldi DS and DP were within the similarity range (86-116%) which indicated that apoptosis activities of all Imraldi are highly similar to EU Humira.
FcγRIa binding assay	The FcγRIa binding activities of Imraldi and the reference products were determined by FRET assay. The binding activity of the Imraldi DS and

Study title	Key findings
	DP ranged from 89 to 106% relative to the bioassay standard. The binding activity of EU Humira ranged from 99 to 107%. FcγRIa binding activities of all the Imraldi DS and DP were within the similarity range (85-113%) which indicated that FcγRIa binding activities of Imraldi are highly similar to EU Humira.
FcγRIIa binding assay	The FcγRIIa binding activities of Imraldi and the reference product were determined by the Alphascreen®-based binding assay. The binding activity of Imraldi DS and DP ranged from 80 to 124% relative to the bioassay standard. The binding activity of EU Humira ranged from 119 to 127%. FcγRIIa binding activities of all the Imraldi DS and DP were within the similarity range (67-141%) which indicated that FcγRIIa binding activities of the Imraldi are highly similar to EU Humira.
FcγRIIb binding assay	The FcγRIIb binding activities of Imraldi and the reference products were determined by the Alphascreen®-based binding assay. . The binding activity of Imraldi DS and DP ranged from 91 to 105% relative to the bioassay standard. The binding activity of EU Humira ranged from 99 to 103%. FcγRIIb binding activities of all the Imraldi DS and DP were within the similarity range (69-149%) which indicated that FcγRIIb binding activities of the Imraldi are highly similar to EU Humira.
FcγRIIIa binding assay (158V/V)	The FcγRIIIa binding activities of Imraldi and the reference products were determined by an Alphascreen® - based binding assay The binding activities of Imraldi DS and DP ranged from 91 to 116% relative to the bioassay. The binding activity of EU Humira ranged from 99 to 122%. FcγRIIIa activities of all the Imraldi DS and DP were within the similarity range (88-124%) which indicated that FcγRIIIa binding activities of the Imraldi are highly similar to EU Humira
FcRn binding assay	The FcRn binding activities of Imraldi and the reference products were determined by the Alphascreen® based binding assay. The FcRn binding activities of Imraldi DS and DP ranged from 82 to 111% relative to the bioassay standard (either of pooled lots of US Humira, Lot: 1010535 and 1017238 or 1021488, 1028011 and 1032716). The FcRn binding activity of EU Humira ranged from 94 to 101%. FcRn binding activities of all the Imraldi DS and DP were within the similarity range (78-121%), which indicated that FcRn binding activities of the Imraldi are highly similar to EU Humira.
C1q binding assay	C1q binding activity was determined by a sandwich enzyme-linked immunosorbent assay (ELISA) method. The binding activities of Imraldi DS and DP ranged from 76 to 103% relative to the bioassay . The binding activity of EU Humira ranged from 98 to 103%. C1q binding activities of all the Imraldi DS and DP were within the similarity range (74-118%) which indicated that C1q binding activities of the Imraldi are highly similar to EU Humira.
ADCC assay using NK92-CD16 cell line	The ADCC assay for Imraldi and the reference products was performed using 3T3 mTNF-α target cells, a mouse fibroblast cell line with NK92-CD16, a human natural killer cell line expressing CD16, used as effector cells. The ADCC activities of the Imraldi DS and DP ranged from 82 to 123% relative to the bioassay standard. The ADCC activity of EU Humira ranged from 95 to 119%. ADCC activities of all the Imraldi DS and DP

Study title	Key findings
	were within the similarity range (78-143%) which indicated that ADCC activities of the Imraldi are highly similar to EU Humira.
CDC assay	The CDC assay for Imraldi and the reference products was performed using Jurkat mTNF-α cell, a T lymphocyte cell line with human transmembrane TNF-α overexpressed and human serum as a complement source. The CDC activities of the Imraldi DS and DP ranged from 89 to 101% relative to the bioassay standard. The CDC activity of EU Humira ranged from 101 to 110%. CDC activities of all the Imraldi DS and DP were within the similarity range (86-110%), which indicated that CDC activities of the Imraldi are highly similar to EU Humira.
Apoptosis assay in *in vitro* IBD model	Apoptosis activity of Imraldi and the reference products was measured through a cell based assay using a colon cancer cell line, HCT 116. The apoptosis activity of Imraldi DP ranged from 92 to 99% relative to the bioassay standard. The apoptosis activity of EU Humira ranged from 97 to 102. Relative activities of the Imraldi DP were within the mean ±3 SD range (93-105%) of the reference products except for one batch of Imraldi with slightly lower activity (92%) than that of EU Humira. However, the difference was within assay variability for apoptosis assay in *in vitro* IBD model. Therefore, apoptosis activity of Imraldi was similar to that of EU Humira.
Inhibition of IL-8 cytokine release in *in vitro* IBD model	Inhibition of IL-8 cytokine release in *in vitro* IBD model of Imraldi and the reference products were assessed. The inhibition activity of Imraldi DP ranged from 96 to 108% relative to the bioassay. The inhibition activity of EU Humira ranged from 96 to 110%. Relative activities of all the Imraldi DP were within the mean ±3 SD range (84-116%) of reference product. These results support the inhibition of IL-8 cytokine release activity in *in vitro* IBD model of Imraldi and Humira are highly similar.
Inhibition of sVCAM-1 adhesion molecule expression	Expression level of sVCAM-1 was measured to determine whether there is any significant difference in their inhibitory effects on TNF-α –induced-adhesion molecule expression in endothelial cells between Imraldi and the reference products. The inhibition activity of Imraldi DP was 104-122% relative to the bioassay standard. The inhibition activity of EU Humira ranged from 101 to 123%. Relative inhibition activities of all the Imraldi DP were within the mean ±3 SD range (81-139%) of reference product. The results support the inhibitory activities of sVCAM-1 expression of Imraldi was similar to that of EU Humira.
Transmembrane TNF-α binding assay	Flow cytometry was used to determine whether there is any significant difference in transmembrane TNF-α binding between Imraldi and the reference products. The binding activity of Imraldi DP ranged from 87 to 99% relative to the bioassay standard. The binding activity of EU Humira ranged from 87 to 109%. Relative binding activities of all the Imraldi DP were within the mean ±3 SD range (73-118%) of reference products. These results support the transmembrane TNF-α binding activity of Imraldi and Humira are highly similar.
Evaluation of regulatory macrophage induction function	Two sets of experiments were performed to determine whether there is any significant difference between Imraldi and the reference products in terms of regulatory macrophage function associated with IBD. In first experiment, regulatory macrophages induced by the treatment of Imraldi

Study title	Key findings
	and the reference products in a two-way mixed lymphocyte reaction (MLR) were confirmed by a regulatory macrophage-specific marker (anti-human CD206). In the second experiment, T-cell anti-proliferation activity by Imraldi and the reference products in two-way MLR was evaluated to confirm the capability of induced regulatory macrophages. As a result of the regulatory macrophage induction assay, the relative activity of Imraldi DP ranged from87 to 100% relative to the bioassay standard (Pooled lots of US Humira, Lot: 1021488, 1028011 and 1032716). The relative activity of EU Humira ranged from 90 to 104 %. Relative activities of all the Imraldi DP were within the mean ±3 SD range (81-112 %) of reference products. As a result of the T cell anti-proliferation assay, the relative activity of all Imraldi DP ranged from 17 to 32% relative to the negative control (IgG isotype control). The relative activity of EU Humira ranged from 20 to 34%. Relative activities of all the Imraldi DP were within the mean ±3 SD range (9-41%) of reference products. These results support the regulatory macrophage induction activity of Imraldi and EU Humira are highly similar.
FcγRIIIa binding assay (158F/F)	FcγRIIIa (F/F type) assay utilized surface plasmon resonance (SPR) technology to determine the binding affinity constant (M) of Imraldi and the reference products. The binding affinity of Imraldi DP range from 1.65E-06 to 1.86E-06 M. The binding affinity of EU Humira ranged from 1.51E-06 to 1.71E -06 M. Binding affinities of all the Imraldi DP were within the mean ±3 SD range (1.31E-06-1.92E-06 M) of reference products. These results support that the binding affinity to FcγRIIIa binding assay (158F/F) of Imraldi and Humira are highly similar.
FcγRIIIb binding assay	FcγRIIIb binding assay utilized SPR technology to determine the binding affinity constant (M) of Imraldi and the reference products. The binding affinity of Imraldi DP ranged from 9.73E-06 to 1.06E-05M. The binding affinity of EU Humira ranged from 8.35E-06 to 9.26E-06M. Binding affinities of Imraldi DP were within the mean ±3 SD range (7.96E-06-1.01E-05M) of reference products, except 2 batches of Imraldi DP. SPR is a highly sensitive method, so binding affinities are generally understood by differences of an order of magnitude (5- to 10- fold). In addition, %CV of bioassay standard (Pooled lots of US Humira· Lot: 1021488, 1028011 and 1032716) used in the FcγRIIIb binding affinity measurement was about 8% and the observed difference in binding affinities between Imraldi DP and upper margin of mean ±3 SD range (1.01E-05 M) was less than 8%. Therefore, the minor difference detected by high sensitive SPR method in 2 batches of Imraldi DP is within the assay variability and unlikely to be physiologically meaningful. These results support the binding affinities to FcγRIIIb of Imraldi and Humira are similar.

Study title	Key findings
Antibody confirmation array	Antibody conformational array was performed using HumiBridge ELISA kit in a sandwich ELISA format consists of a pool of 34 antibodies raised against peptides derived from the full-length protein sequence of adalimumab. The OD difference between Imraldi and Humira was less than 50%, suggesting that the difference between Imraldi and Humira is lower than 0.1% in terms of conformational structure. When binding profile is similar between Imraldi and Humira across all peptide antibodies, it supported that Imraldi is similarly folded and glycosylated compared to Humira and that the conformational structure is similar between Imraldi and Humira.
TNF-β (LTα3) binding assay	LTα3 binding activity of Imraldi and the reference products was determined by a FRET assay. Compared to etanercept, Imraldi and EU Humira showed no signal, demonstrating a significant lack of LTα3 binding activity. Etanercept was analysed concurrently as a positive control.

An *in vivo* pharmacodynamic (PD) study have been performed, as summarised in Table SII.3 to demonstrate the PD, efficacy, and safety of Imraldi in comparison to US-sourced Humira (Study No. BMC394) and one non-clinical study as summarised in Table SII.1 has been performed to evaluate the toxicology profiles of US-sourced Humira in cynomolgus monkeys (Study No. 2064-008).

A PD study in Tg197 transgenic mice was performed to evaluate the similarity of Imraldi and Humira in terms of therapeutic efficacy following administration at dose levels of 0.5, 3, and 10 mg/kg twice per week for 7 weeks. From this study, no significant differences were observed. The key findings from this study is summarised in Table SII.3 below.

Table SII.3: Summary of comparative in vivo pharmacodynamics study

Study title	Key findings
PD Study of SB5 in Tg197 transgenic mouse model (BMC 394)	Following intraperitoneal administration of 0.5, 3, and 10 mg/kg Imraldi or US-sourced Humira twice a week for 7 weeks to seven groups of Tg197 transgenic mice (n=10 per group, 3 weeks of age), the efficacy was evaluated based on the changes of *in vivo* arthritis scores and histopathology scores at 10 weeks of age. There were no significant differences in *in vivo* arthritic scores and changes of histopathology scores between Imraldi and US-sourced Humira.

Based on the studies on the safety of Imraldi, there was no safety concern identified from pre-clinical data. In a 4-week repeated dose toxicity study in cynomolgus monkeys, Imraldi and US-sourced Humira were well tolerated and their toxicity profile was similar.

Since Imraldi is being developed as a biosimilar product to the reference product Humira, no additional non-clinical data are considered necessary.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Safety data of Imraldi are available from 5 clinical studies:

- Study SB5-G11-NHV, a randomised, single-blind, three-arm, parallel group, single-dose study to compare the pharmacokinetics, safety, tolerability, and immunogenicity of three formulations of adalimumab (SB5, EU-sourced Humira, and US-sourced Humira) in healthy subjects.
- Study SB5-G12-NHV, a randomised, open-labelled, two-arm, parallel group, single-dose study to compare the pharmacokinetics, safety, and tolerability of the pre-filled pen and pre-filled syringe of SB5 in healthy subjects.
- Study SB5-1003, a randomised, single-blind, two-arm, parallel group, single-dose study to compare the pharmacokinetics, safety, tolerability, and immunogenicity of two formulations of SB5 in healthy male subjects.
- Study SB5-G21-RA, an open-labelled, single-arm, multicentre clinical study to evaluate the usability and safety of the pre-filled pen and pre-filled syringe of SB5 in subjects with rheumatoid arthritis.
- Study SB5-G31-RA, a randomised, double-blind, parallel group, multicentre clinical study to evaluate the efficacy, safety, tolerability, pharmacokinetics, and immunogenicity of SB5 compared to Humira in subjects with moderate to severe rheumatoid arthritis despite methotrexate therapy.

Exposure data from the 5 studies are presented separately. The data from the healthy volunteer studies (SB5-G11-NHV, SB5-G12-NHV and SB5-1003) are summarised in the paragraphs below and not presented in tables as subjects of this study only received a single dose of adalimumab.

In the study SB5-G11-NHV, a total of 189 healthy subjects were randomised in a 1:1:1 ratio into 3 arms to receive a single 40 mg subcutaneous dose of Imraldi (n=63), EU-sourced Humira (n=63), or US-sourced Humira (n=63). The subjects were followed up for 71 days after the administration of adalimumab for pharmacokinetic (PK) assessment and safety monitoring. The majority of the subjects who received Imraldi were male (n=59 [93.7%]) and all except 2 subjects (n=61 [96.8%]) were white. The age of subjects exposed to Imraldi ranged from 18 to 55.

In the study SB5-G12-NHV, a total of 190 healthy subjects aged 18-55 years (inclusive) were randomised in a ratio of 1:1 to receive a single 40 mg subcutaneous dose of Imraldi via pre-filled pen (n=95) or PFS (n=95). The subjects were followed for approximately 8 weeks after administration of Imraldi during which the PK and safety measurements were performed. The majority of the subjects in this study were male (n=171 [90.0%]) and white (n=158 [83.2%]).

In the study SB5-1003, a total of 188 healthy male subjects aged 18-55 years were randomised in a 1:1 ratio into 2 arms to receive a single subcutaneous dose of either 40 mg/0.4mL of SB5 or 40 mg/0.8mL of SB5. The subjects were followed up for 57 days after the administration of SB5 for pharmacokinetics, safety, tolerability, and immunogenicity measurements. The majority of the subjects in this study were white (n=179 [95.2%]).

In the study SB5-G21-RA, a total of 49 subjects with rheumatoid arthritis aged 23-55 years received 40 mg subcutaneous dose of Imraldi PFS at week 0 and week 2, followed by 40 mg subcutaneous dose

of Imraldi PFP at week 4 and then EOW thereafter up to Week 10. The pain score of the subjects were followed up at week 2 and week 6 using 11-point numeric rating scale for usability and safety assessment of the PFP and PFS of SB5 in subjects with RA. The majority of the subjects were female (n=39 [79.6%]) and all subjects were white.

In the study SB5-G31-RA, a total of 544 subjects with moderate to severe RA who had had an inadequate response to methotrexate (MTX) and who had been on the stable dose of MTX for at least 4 weeks prior to screening were randomised at Week 0 in a 1:1 ratio to receive either Imraldi 40 mg (n=271) or Humira 40 mg (n=273) every other week. At Week 24, subjects who were receiving Humira were randomised again in a 1:1 ratio to either continue with Humira 40 mg or be transitioned to Imraldi 40 mg every other week up to Week 50. Imraldi or Humira was co-administered with oral or parenteral MTX (10-25 mg/week) and folic acid (5-15 mg/week).

Exposure to Imraldi in the study SB5-G31-RA is summarised by duration of exposure in Table SIII.1, by age group and gender in Table SIII.2, and by ethnic or racial origin in Table SIII.3. The total exposure from clinical trial for Imraldi is approximately 304.910 patient-years (Table SIII. 1). Since all subjects received the same dose of Imraldi (40 mg), exposure data is not represented based on dose. Special populations (e.g., pregnant women, lactating women, renal impairment, hepatic impairment, cardiac impairment, and immunocompromised) were excluded from the study and thus the exposure data was not represented for these populations.

Table SIII. 1: Duration of exposure

Indication: Rheumatoid Arthritis		
Duration of exposure	**Patients**	**Person time**
Up to 3 months	393	96.825
3-6 months	378	92.868
6-9 months	283	62.521
9-12 months	248	52.696
Total	**393**	**304.910**

Table SIII. 2: Age group and gender

Age group	**Patients**		**Person time**	
	M	**F**	**M**	**F**
< 65 years	70	280	57.775	215.233
≥ 65 to < 75 years	4	38	3.403	27.537
≥ 75 years	0	1	N/A	0.962
Total	**74**	**319**	**61.178**	**243.732**

Table SIII. 3: Ethnic origin

Ethnic origin	**Patients**	**Person time**
White	391	303.899
Asian	2	1.011
Total	**393**	**304.910**

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

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

The clinical development programme for Imraldi as a biosimilar to Humira (adalimumab) comprised of two Phase I studies and a Phase III study. The first study was a randomised, single-blind, three-arm, single-dose study to compare the PK, safety, tolerability, and immunogenicity of SB5, EU-sourced Humira, and US-sourced Humira in healthy adult subjects (study SB5-G11-NHV). The second study was a Phase I, randomised, open-labelled, two-arm, parallel group, single-dose study to compare the PK, safety, tolerability, and immunogenicity of the pre-filled pen and PFS of SB5 in healthy subjects (study SB5-G12-NHV). The third study was a Phase III, randomised, double-blind, parallel group, multicentre clinical study to evaluate the efficacy, safety, PK, and immunogenicity of SB5 compared to Humira in subjects with moderate to severe RA despite MTX therapy (study SB5-G31-RA).

In the two Phase I healthy volunteer studies, inclusion and exclusion criteria were designed to ensure that the study population were healthy and homogenous to clarify any risks associated with the study and enable appropriate comparison of the PK, safety, tolerability, and immunogenicity of SB5 and Humira. Healthy female subjects of non-childbearing potential or healthy male subjects aged 18-55 years with all screening results within the normal range (or outside the normal range but not clinically significant) were included in the study. The following conditions or disorders that could increase the risks of the study or confound evaluations were excluded:

- History and/or current presence of clinically significant atopic allergy (e.g., asthma, urticaria, angioedema, eczematous dermatitis), hypersensitivity, or allergic reactions (either spontaneous or following drug administration), also including known or suspected clinically relevant drug hypersensitivity to any components of the test and reference investigational product (IP) formulation or comparable drugs.
- Active or latent tuberculosis (TB) (as indicated by a positive test result for Mycobacterium Tuberculosis) or who had a history of TB.
- History of invasive systemic fungal infections (e.g., histoplasmosis) or other opportunistic infections judged relevant by the Investigator, including local fungal infections or a history of herpes zoster.
- Any systemic or local infection, a known risk for developing sepsis and/or known active inflammatory process within 6 months prior to IP administration. Subjects with C-reactive protein (CRP) > 1.5 times the upper limit of normal (ULN) at Screening or Day -1 were not enrolled in order to exclude those subjects with chronic inflammatory processes.
- Serious infection (associated with hospitalisation and/or which required intravenous antibiotics) within 6 months prior to IP administration.
- History of and/or current cardiac disease.

- History of and/or current gastrointestinal, renal, hepatic, cardiovascular, haematological (including pancytopenia, aplastic anaemia, or blood dyscrasias), metabolic (including known diabetes mellitus), or pulmonary disease classified as significant by the Investigator.
- History of cancer including lymphoma, leukaemia, and skin cancer.
- Impaired liver function.
- History of immunodeficiency including those subjects with a positive test for human immunodeficiency virus (HIV).
- Illness within 4 weeks prior to screening that is classified as clinically significant by the Investigator.
- Mental disease classified as serious by the Investigator.

Other exclusion criteria included previous treatment with adalimumab, receipt of live vaccine(s) within 30 days prior to screening or requiring live vaccine(s) between screening and final study visit, alcoholic beverage intake of more than 28 units per week, evidence of drug abuse as indicated by a positive urinary drug screening at screening and/or Day -1, intake of medication with a half-life > 24 hours within 4 weeks or 10 half-lives of the medication prior to IP administration, donation of > 100 mL blood within 4 weeks prior to IP administration, participation in another study with an investigational drug within 4 weeks prior to IP administration, receipt of a biological or immunosuppressive agent within 3 months of screening, subjects who were not able to consume standardised meals provided by the clinical study site during hospitalisation, subjects who were not likely to complete the study, anyone directly involved in the conduct of the study (or a relative thereof), vulnerable subjects, or pregnant and nursing women.

The Phase III clinical study included male or female patients aged 18-75 years who had been diagnosed (at least 6 months but not exceeding 15 years prior to screening) as having moderate to severe active RA despite MTX therapy and who had been treated with MTX for at least 6 months prior to randomisation and were on stable dose of MTX (10-25 mg/week) for at least 4 weeks prior to screening. Female subjects were only included if they are not pregnant or nursing at the time of screening and were not planning to become pregnant from screening until 5 months after the last dose of IP.

In general, exclusion criteria included any major illness/condition or any serious disorder that would increase the risks associated with the study or confound the evaluation of the effect of Imraldi treatment. These included the following conditions/disorders:

- History of congestive heart failure (CHF) (New York Heart Association [NYHA] Class III/IV).
- History of acute myocardial infarction (MI) or unstable angina within the previous 12 months prior to Screening.
- Uncontrolled diabetes mellitus or uncontrolled hypertension which, in the opinion of the Investigator, would have put the subject at risk if they were enrolled.
- History of demyelinating disorders (such as multiple sclerosis [MS] or Guillain-Barré syndrome).

- History of any malignancy within the previous 5 years prior to Screening except completely excised and cured squamous carcinoma of the uterine cervix, cutaneous basal cell carcinoma (BCC), or cutaneous squamous cell carcinoma.
- History of lymphoproliferative disease including lymphoma.
- History of organ transplantation.
- Significant systemic RA involvement (e.g., vasculitis, pulmonary fibrosis, etc.) which, in the opinion of the Investigator, would have put the subject at risk if they were enrolled.
- Other inflammatory or rheumatic diseases, including but not limited to PsA, AS, systemic lupus erythematosus (SLE), Lyme disease, or fibromyalgia, which may have confounded the evaluation of the efficacy or safety of IP.
- Any conditions significantly affecting the nervous system (e.g., neuropathic conditions or nervous system damage) which may have interfered with the Investigator's assessment on disease activity scores including joint counts.
- Any other disease or disorder which, in the opinion of the Investigator, would have put the subject at risk if they were enrolled.
- Positive serological test for hepatitis B or hepatitis C or a known history of infection with HIV.
- Active TB, recent exposure to TB or evidence of latent TB.

  However, subjects who have positive QuantiFERON® Gold test results after Randomisation but do not have any evidence of active TB may continue in the study at the discretion of the Investigator if the subjects initiate anti-latent TB therapy according to country-specific guideline prior to or simultaneously with the administration of further IP.
- History of serious infection or treatment with antibiotics for an infection within 8 weeks (IV) or 2 weeks (oral) prior to randomisation.
- History of chronic or recurrent infection.
- History of an infected joint prosthesis which had not been removed or replaced.

Other exclusion criteria included known hypersensitivity to human Ig proteins or other components of Imraldi or Humira, previous treatment with any biological agents including TNF inhibitors, treatment with prohibited concomitant medications within the timeframe specified (including live/live-attenuated vaccine within 8 weeks prior to Randomisation or during the study), abnormal hepatic or renal function at Screening, abnormal haematologic parameters at Screening, had physical incapacitation (American College of Rheumatology [ACR] functional Class IV or wheelchair-/bed-bound), or had any substance abuse problem within the previous 3 years prior to Screening.

During the study periods, 'importance' of individual exclusion criterion was not discussed. Also, whether or not each criterion is subject for 'missing information' was not assessed. Instead, as a biosimilar of Humira, missing information of Imraldi is aligned with that of the reference product, based on the European Medicines Agency (EMA) guide on similar biological medicinal products. Missing information of Imraldi is listed below.

- Episodic treatment in UC

- Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD
- Long-term safety information in the treatment of children aged from 6 years to less than 18 years with UC

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/very rare adverse reactions, adverse reactions with a prolonged exposure/long latency, dose-related reactions, and the reactions occur in other claimed indications (JIA, axial spondyloarthritis, PsA, PsO, HS, CD, UC, and uveitis).

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

Table SIV.3: Exposure of special populations included or not in clinical trial development programmes

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td>Children</td><td>Not included in the clinical development program</td></tr>
<tr><td>Elderly</td><td>
<table>
<tr><th rowspan="2">Age group</th><th colspan="2">Patients</th><th colspan="2">Person Time</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td>≥ 65 to < 75 years</td><td>4</td><td>38</td><td>3.4</td><td>27.5</td></tr>
<tr><td>≥ 75 years</td><td>0</td><td>1</td><td>N/A</td><td>1.0</td></tr>
<tr><td>Total</td><td>4</td><td>39</td><td>3.4</td><td>28.5</td></tr>
</table>
</td></tr>
<tr><td>Pregnant women</td><td>Not included in the clinical development program</td></tr>
<tr><td>Breastfeeding women</td><td>Not included in the clinical development program</td></tr>
<tr><td>Patients with relevant comorbidities:
Patients with hepatic impairment
Patients with renal impairment
Patients with cardiovascular impairment (including NYHA class III or IV CHF)
Patients with other relevant co-morbidity (including history of organ transplantation)
Immunocompromised patients
Patients with a disease severity different from inclusion criteria in clinical trials</td><td>Not included in the clinical development program</td></tr>
</table>

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td>Population with relevant different ethnic origin</td><td>
<table>
<tr><th>Ethnic Origin</th><th>Patients</th><th>Person Time</th></tr>
<tr><td>White</td><td>391</td><td>303.9</td></tr>
<tr><td>Asian</td><td>2</td><td>1.0</td></tr>
<tr><td>Total</td><td>393</td><td>304.9</td></tr>
</table>
</td></tr>
<tr><td>Subpopulations carrying relevant genetic polymorphisms</td><td>Not included in the clinical development program</td></tr>
</table>

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Imraldi sales data was obtained from the marketing partners from the date of launch to Aug 12, 2021. Imraldi had been marketed only in a 40 mg/0.8 ml formulation as either PFS, PFP. Exposure was estimated using the WHO Defined Daily Dose (DDD) for adalimumab (2.9 mg/day).

SV.1.2 Exposure

Cumulatively from the International Birth Date (IBD) through Aug 12, 2021, there were about [redacted] patient-years (PYs) of treatment for Imraldi.

Table SV.1: Exposure table by region

Region	Units Sold (PFP or PFS)	Estimated Exposure (Person-Years)
EU	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

There is no anticipated potential for illegal use of adalimumab given its mechanism of action.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

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

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

Not applicable as the risks are aligned with those of the reference product.

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

Based on the EMA guide on similar biological medicinal products, the RMP should take into account the risks associated with the use of the reference product. The following risks are the safety concerns of both Imraldi and the reference product, Humira.

Important identified risks	Important potential risks	Missing information
• Serious infections • Tuberculosis (TB) • Malignancies • Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis) • BCG disease following live BCG vaccination in infants with *in utero* exposure to Imraldi	• Progressive multifocal leukoencephalopathy (PML) • Reversible posterior leukoencephalopathy syndrome (RPLS) • Adenocarcinoma of colon in ulcerative colitis (UC) patients	• Patients with immune-compromised conditions • Episodic treatment in PsO, UC and juvenile idiopathic arthritis (JIA) • Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD • Long-term safety information in the treatment of children with uveitis • Long-term safety information in the treatment of children aged from 6 years to less than 18 years with UC

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

- The missing information “Patients with immune compromised conditions”, Long-term safety information in the treatment of children with uveitis” are removed from the list of safety concerns to align with that of the reference product

  Reasons for removal: To align the safety concerns of Imraldi with those of the reference product Humira.

- The missing information “Episodic treatment in Ps, UC and JIA reclassified to Episodic treatm ent in UC is reclassified to align with that of the reference product.

  Reason for reclassification: To align the safety concerns of Imraldi with those of the reference product Humira.

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

Based on the EMA guide on similar biological medicinal products, the RMP should take into account identified and potential risks associated with the use of the reference product. Therefore, this section will contain all the important identified risks and important potential risks described in the RMP for the reference product, Humira, and from the scientific literature.

The SB5-G31-RA study was conducted in patients with moderate to severe RA. There was no safety concern newly detected from this study and it has been concluded that the Imraldi safety profile was comparable with that of Humira.

The reference product, Humira, has been used in clinical practice for more than 10 years and the risk profile is well known.

For each risk presented in this section, the clinical trial safety database was searched for specified events using Standardised Medical Query (SMQ)/high level group terms (HLGTs), PTs, high level terms (HLTs), and search stems for that risk based on the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0. (Refer to Annex 7 for the specific adverse event terms and/or stems used for risks analysis)

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

SVII.3.1.1 Important identified risk

Serious infections

Potential mechanisms: Adalimumab may alter T-cell mediated immunity through modulation of TNF-α.

Evidence source(s) and strength of evidence: Study SB5-G31-RA; Imraldi SmPC, Section 4.4 ‘Special warnings and precautions for use’; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

- Frequency with 95% CI:
  Frequency in the Imraldi clinical study (SB5-G31-RA)
  There were 4 events of serious infections in 4 patients treated with Imraldi (subject incidence: 1.018%; 95% CI: 0.278, 2.585) corresponding to an exposure-adjusted event rate of 1.312 events per 100 patient-years (95% CI: 0.357, 3.359). There were 4 events of serious infection in 4 patients treated with Humira (subject incidence: 1.465%; 95% CI: 0.401, 3.709), and the corresponding exposure-adjusted event rate was 2.242 events per 100 patient-years (95% CI: 0.611, 5.741).

Table SVII.3.1.1.1 Subject incidence and exposure-adjusted rate of serious infections

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Imraldi	393	4 (1.018)	0.278, 2.585	304.910	4	1.312	0.357, 3.359
Humira	273	4 (1.465)	0.401, 3.709	178.395	4	2.242	0.611, 5.741

[a] Subject incidence = N1/N × 100.

[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

- Seriousness/outcomes:
  There were 4 events (viral infection, Escherichia urinary tract infection, urinary tract infection, and pneumonia) of serious infections in 4 patients treated with Imraldi (subject incidence: 1.018%; 95% CI: 0.278, 2.585) corresponding to an exposure-adjusted event rate of 1.312 events per 100 patient-years (95% CI: 0.357, 3.359). Four events (bronchopneumonia, staphylococcal sepsis, bronchitis, and pneumonia) of serious infection in 4 patients were reported to be serious in patients treated with Humira (subject incidence: 1.465%; 95% CI: 0.401, 3.709), and the corresponding exposure-adjusted event rate was 2.242 events per 100 patient-years (95% CI: 0.611, 5.741).

Table SVII.3.1.1.2 Subject incidence and exposure-adjusted rate of serious infections that were serious adverse events (SAEs)

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Imraldi	393	4 (1.018)	0.278, 2.585	304.910	4	1.312	0.357, 3.359
Humira	273	4 (1.465)	0.401, 3.709	178.395	4	2.242	0.611, 5.741

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Of the 4 serious infections reported from the Imraldi treatment group, all 4 events were recovered. Of the 4 serious infections reported from the Humira treatment group, 3 events were recovered and 1 event (staphylococcal sepsis) was recovering at the time of IP discontinuation. There was no serious case of diverticulitis and opportunistic infections including invasive fungal infections, parasitic infections, legionellosis, and TB.

- Severity and nature of risk:
  In the Imraldi treatment group, 2 events (urinary tract infection and pneumonia) of serious infection were reported to be severe in severity (0.656 events per 100 patient-years; 95% CI: 0.079, 2.369). In the Humira treatment group, 2 events (bronchopneumonia and staphylococcal sepsis) of serious infections were reported to be severe in severity (1.121 events per 100 patient-years; 95% CI: 0.136, 4.050).

Table SVII.3.1.1.3 Subject incidence and exposure-adjusted rate of serious infections that were severe

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Imraldi	393	2 (0.509)	0.062, 1.826	304.910	2	0.656	0.079, 2.369
Humira	273	2 (0.733)	0.089, 2.621	178.395	2	1.121	0.136, 4.050

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

- Impact on individual patient:
  Serious infections can influence the patient's quality of life and overall health. Some of these infections might lead to hospitalisation, long-lasting antimicrobial therapy, and sometimes even result in death.

Risk factors and risk groups: Factors that increase the risk of infection include steroids or other medications that suppress the immune system, such as anti-rejection drugs for a transplanted organ, HIV or acquired immune deficiency syndrome (AIDS), certain types of cancer or other disorders that affect the immune system, implanted medical devices, malnutrition, and increased age.[4]

While taking Imraldi, the risk of infection might increase particularly in patients over 65 years of age, taking immunosuppressive treatment, heavy smokers, or who have a history of decreased lung function. Infections may be serious and, in rare cases, life-threatening.

Preventability: Having a high degree of suspicion with prompt treatment of signs or symptoms of infection, even in the absence of fever. Using the minimum amount of immunosuppressive drugs to accomplish and sustain remission.

Impact on the risk-benefit balance of the product: Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place.

Public health impact: There is no potential public health risk or impact.

Tuberculosis

Potential mechanisms: Adalimumab may alter T-cell mediated immunity through modulation of TNF-α.

Evidence source(s) and strength of evidence: Study SB5-G31-RA; Imraldi SmPC, Section 4.4 'Special warnings and precautions for use'; and referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

- Frequency with 95% CI: Only clinically active TB infections are presented (TB test positivity alone, or latent TB, are not included).

  Frequency in the Imraldi clinical study (SB5-G31-RA): There was no case of TB.

- Seriousness/outcomes: There was no case.
- Severity and nature of risk: Risk severity ranges from mild infectious processes to sepsis and death.
- Impact on individual patient: Clinically active TB can influence the patient's quality of life and overall health, sometimes resulting in death.

Risk factors and risk groups: Factors that increase the risk of infection include steroids or other medications that suppress the immune system, such as anti-rejection drugs for a transplanted organ, HIV or acquired immune deficiency syndrome (AIDS), certain types of cancer or other disorders that affect the immune system, implanted medical devices, malnutrition, and increased age.[4]

Preventability: All patients must be screened for latent TB before initiating adalimumab.[5]

Impact on the risk-benefit balance of the product: Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place.

Public health impact: The potential public health issue is that of increased rates of TB and, therefore, increased possible risk of contagion. TB is highly contagious via airborne bacteria, unlike other infections which are not likely to be transmitted by casual contact with an infected individual.

Malignancies

Potential mechanisms: Adalimumab may alter T-cell mediated immunity, which may influence the occurrence of malignancy, but the mechanism is unknown.

Evidence source(s) and strength of evidence: Study SB5-G31-RA; Imraldi SmPC, Section 4.4 'Special warnings and precautions for use'; and referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

- Frequency with 95% CI: Frequency in the Imraldi clinical study (SB5-G31-RA)
  There were no reports of the following malignancies (previously classified as important identified risks) leukaemia, hepatosplenic T-cell lymphoma (HSTCL), non-melanoma skin cancer (NMSC), melanoma, Merkel cell carcinoma in either the Imraldi or Humira treatment groups.
  There were no events of lymphoma in patients treated with Imraldi. There was 1 event of lymphoma in 1 patient treated with Humira (subject incidence: 0.366%; 95% CI: 0.009, 2.024) corresponding to an exposure-adjusted event rate of 0.561 events per 100 patient-years (95% CI: 0.014, 3.123).

Table SVII.3.1.1.4 Subject incidence and exposure-adjusted rate of lymphoma

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Imraldi	393	0	N/A	N/A	N/A	N/A	N/A
Humira	273	1 (0.366)	0.009, 2.024	178.395	1	0.561	0.014, 3.123

[a] Subject incidence = N1/N × 100.

[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

- Seriousness/outcomes: Imraldi clinical study (SB5-G31-RA)
  The event of lymphoma in the Humira treatment group was reported to be serious (0.561 events per 100 patient-years; 95% CI: 0.014, 3.123).

Table SVII.3.1.1.5. Subject incidence and exposure-adjusted rate of lymphoma that were SAEs

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Imraldi	393	0	N/A	N/A	N/A	N/A	N/A
Humira	273	1 (0.366)	0.009, 2.024	178.395	1	0.56056	0.014, 3.123

[a] Subject incidence = N1/N × 100.

[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

The one serious event in the Humira treatment group was not resolved.

- Severity and nature of risk:
  The risk for lymphoma, leukaemia, and HSTCL includes death. The risk for NMSC includes disfigurement, and possibly death in rare cases of metastatic squamous cell skin cancer. The risk for melanoma includes disfigurement, death and metastatic disease. The risk for MCC includes metastatic disease and death.
- Impact on individual patient:

  Malignancies can directly affect the patient's physical functioning and lifespan and have a severe effect on the patient's quality of life. Potential effects will depend on the individual patient and other factors including tolerance to treatment and degree of social and emotional

support. The gravity of the diagnosis and fear about the effects of malignancy can also cause psychological distress.

Risk factors and risk groups:

- Lymphoma

There is an increased background risk for lymphoma and leukaemia in RA patients with long-standing, highly active, inflammatory disease.[5]

Studies by Askling et al. and Baecklund et al. have shown that patients with RA have an approximately 2-fold increased risk of lymphoma and leukaemia. The increase in lymphoma risk is limited to those RA patients who have long standing and very severe disease.[6,7]

In a prospective study designed to determine the rate of lymphoma among patients with RA, those who developed lymphoma (irrespective of treatment) were significantly older, had more comorbidities, were more likely to be male, had more education, and were more likely to be non-Hispanic whites compared with those that did not develop lymphoma.[8]

Factors that increase the risk of HL include age (from 15 to 30 years as well as older than 55 years), a family history of lymphoma, being a male, previous Epstein-Barr virus infection, and a weakened immune system (such as from HIV/AIDS or certain medications after organ transplant).[9]

Factors that may increase the risk of NHL include medications that suppress the immune system, infections with certain viruses and bacteria (such as HIV, Epstein-Barr virus, ulcer-causing Helicobacter pylori), and older age (60 years or older).[10]

- Hepatosplenic T-cell lymphoma (HSTCL)

Some of these HSTCLs with adalimumab have occurred in young adult patients on concomitant treatment with azathioprine (AZA) or 6-mercaptopurine (6-MP) used for IBD. The potential risk with the combination of AZA or 6-MP and adalimumab should be carefully considered.[5]

Additionally, thiopurine therapy in patients with IBD, combined immunosuppression, age groups from 10 to 35 years, and the male sex are considered to be risk factors of HSTCL.[11,12]

- Leukaemia

Patients with long-standing, highly active, inflammatory disease, and those with a history of malignancy are at an increased risk of developing leukaemia after treatment with a TNF-antagonist. Caution should also be exercised in considering treatment of patients with increased risk for malignancy due to heavy smoking or chronic obstructive pulmonary disease.[5]

Factors with an increased risk of leukaemia include previous chemotherapy and radiation therapy, certain genetic disorders (such as Down syndrome), exposure to certain chemicals (such as benzene), smoking, and a family history of leukaemia.[13]

- Non-melanoma skin cancer (NMSC)

Risk factors of skin cancer include radiation (sunlight or radiation therapy), personal or family history of melanoma, fair skin (having less melanin), certain medical conditions that suppress the immune system, certain medicines (such as some antibiotics, hormones, or antidepressants), and exposure to arsenic at work. In addition, actinic keratosis and HPV infection are also risk factors of skin cancer.[14]

- Melanoma

Among patients considered for TNF-therapy, patients with a history of malignancy, or patients who develop a malignancy during treatment and considering continuation of the treatment. Patients with PsO and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment.[5]

Factors that may increase the risk of melanoma include fair skin (having less melanin), a history of sunburn, a family history of melanoma, excessive ultraviolet (UV) light exposure, many common moles, and a weakened immune system (such as those who have undergone organ transplant).[15]

- Merkel cell carcinoma (MCC)

Factors such as advanced age, immunosuppression (such as organ transplants and HIV), other cancers, and UV light exposure may increase the risk of developing Merkel cell carcinoma.[16]

Preventability:

Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy. Caution should also be exercised in patients with PsO and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment.[5]

Periodic skin examination is recommended, particularly for patients with risk factors for skin cancer.

All patients treated with anti-TNF should be protected against UV radiation and receive a dermatologic examination before starting therapy and once a year thereafter.[17]

For all malignancies, patients are instructed to report to their doctor if they develop symptoms (including fever), skin lesions, and if they are taking AZA or 6-MP in addition to Imraldi.

Impact on the risk-benefit balance of the product:

Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place.

Public health impact:

There is no potential public health risk or impact.

Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis)

Potential mechanisms: TNF blockade augments the number of peripheral T cells which in turn enhances auto-immune responses by changing the function of antigen presenting cells, potentiating signalling of T-cell receptor and/or reducing the apoptosis of autoreactive T-cells. Consequently, these T-cells lead to maturation of B-cells to those secreting autoantibodies to neuronal specific antigens. This sequence of events may lead to development of drug-induced neuropathies.[18]

Evidence source(s) and strength of evidence: Study SB5-G31-RA; Imraldi SmPC, Section 4.8 ‘Undesirable effects’ and Section 4.4 ‘Special warnings and precautions for use’; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

- Frequency with 95% CI: Frequency in the Imraldi clinical study (SB5-G31-RA)
  There were no events of demyelinating disorders in patients treated with Imraldi. There was 1 event of MS in 1 patient treated with Humira (subject incidence: 0.366%, 95% CI: 0.009, 2.024). The event corresponded to an exposure-adjusted event rate of 0.561 events per 100 patient-years (95% CI: 0.014, 3.123).

Table SVII.3.1.1.7 Subject incidence and exposure-adjusted rate of demyelinating disorders

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Imraldi	393	0	N/A	N/A	N/A	N/A	N/A
Humira	273	1 (0.366)	0.009, 2.024	178.395	1	0.561	0.014, 3.123

[a] Subject incidence = N1/N × 100.

[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

- Seriousness/outcomes: The event of MS in the Humira treatment group was reported to be serious (0.561 events per 100 patient-years; 95% CI: 0.014, 3.123).

Table SVII.3.1.1.8 Subject incidence and exposure-adjusted rate of demyelinating disorders that were SAEs

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Imraldi	393	0	N/A	N/A	N/A	N/A	N/A
Humira	273	1 (0.366)	0.009, 2.024	178.395	1	0.561	0.014, 3.123

[a] Subject incidence = N1/N × 100.

[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

The event of MS in Humira treatment group was resolved with sequelae.

- Severity and nature of risk: The event of MS in the Humira treatment group was reported to be severe in severity (0.561 events per 100 patient-years; 95% CI: 0.014, 3.123).

Table SVII.3.1.1.9 Subject incidence and exposure-adjusted rate of demyelinating disorders that were severe

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Imraldi	393	0	N/A	N/A	N/A	N/A	N/A
Humira	273	1 (0.366)	0.009, 2.024	178.395	1	0.561	0.014, 3.123

[a] Subject incidence = N1/N × 100.

[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

- Impact on individual patient: Central and peripheral demyelinating disorders can significantly impact a patient's quality of life due to the severe nature of the symptoms of MS, Guillain-Barré syndrome, and etc. These disorders may lead to patient disability as well as increased morbidity and mortality.

Risk factors and risk groups: Patients with pre-existing MS or Guillain-Barré syndrome belong to the high-risk group. Additionally, first-degree relatives of patients with MS have an increased propensity for developing MS, with a sibling relative risk ranging between 18 and 36.[19] Factors of increased risk of MS include genetic associations (e.g., HLA-DR2 [HLA-DRB1*15]), ethnic origin (e.g., African American men have lower risk than white men), women, Epstein-Barr virus infection, smoking, and latitude/vitamin D.[20]
Factors of increased risk of GBS include men, increased age, viral or bacterial infection (particularly *Campylobacter jejuni* infection), and certain vaccines.[21]

Preventability: Prescribers should exercise caution in considering the use of Imraldi in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders.[5]
In the guidelines for management of PsO and PsA 2008 by the American Academy of Dermatology Inc., it is reported that there is an association between anti-TNF therapy and demyelinating diseases such as MS.[22]

Impact on the risk-benefit balance of the product: Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place.

Public health impact: There is no potential public health risk or impact.

BCG disease following live BCG vaccination in infants with *in utero* exposure to Imraldi

Potential mechanisms: BCG may alter T-cell mediated immunity through modulation of TNF-α.

Evidence source(s) and strength of evidence:
Imraldi SmPC, Section 4.6 'Fertility, pregnancy and lactation' and Section 4.4 'Special warnings and precautions for use'. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

Patients treated with adalimumab may receive concurrent vaccinations, except vaccines with live viruses. It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating adalimumab therapy. Administration of live vaccines (e.g., BCG vaccine) to infants exposed to adalimumab *in utero* is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

Risk factors and risk groups: Infants who are exposed to Imraldi intrauterine.

Preventability: Live vaccines should not be given to patients using Imraldi, and infants exposed to Imraldi *in utero* should not receive live vaccines (e.g., BCG) for 5 months following mother's last Imraldi dose.

Impact on the risk-benefit balance of the product: Appropriate risk minimisation measures have been in place for Humira more than 10 years. In addition, additional risk minimisation measure will be adopted following the reference product. With these measures in place, the benefit-risk balance remains positive.

Public health impact: There is no potential public health risk or impact.

SVII.3.1.2 Important potential risks

PML

Potential mechanisms: Reactivation of Polyomavirus JC, the etiologic agent of PML.

Evidence source(s) and strength of evidence: Referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

- Frequency with 95% CI: Frequency in the Imraldi clinical study (SB5-G31-RA)
  There were no events of progressive multifocal leukoencephalopathy (PML) reported in either Imraldi or Humira treatment group.
- Seriousness/outcomes: There were no events of PML reported in either Imraldi or Humira treatment group.
- Severity and nature of risk: There were no events of PML reported in either Imraldi or Humira treatment group.

- Impact on individual patient: PML can significantly impact a patient's quality of life given the severity of this condition, its life-threatening and often fatal nature, and associated co-morbidities.

Risk factors and risk groups: Immunosuppressive conditions such as HIV/AIDS are the main risk factors of PML. A study conducted by Eng et al. analysed that approximately 41% of the patients with PML were found in the 40 to 49 years age group and the PML patients were predominantly male with a 75% estimate.[23]

HIV infection is the basis of approximately 85% of all PML cases.[24]

Before the HIV epidemic, more than 60% of PML cases were found in patients with lymphoproliferative disorders. Other conditions that are risk factors of PML are hematologic malignancies, organ transplants, and chronic inflammatory diseases.[25,26]

Preventability: There are no preventable measures.

Impact on the risk-benefit balance of the product: Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place.

Public health impact: The potential public health impact is unknown.

RPLS

Potential mechanisms: The potential mechanism is unknown.

Evidence source(s) and strength of evidence: Study SB5-G31-RA; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

- Frequency with 95% CI: Frequency in the Imraldi clinical study (SB5-G31-RA)
  There were no events of reversible posterior leukoencephalopathy syndrome (RPLS) reported in either Imraldi or Humira treatment group.
- Seriousness/outcomes: There were no events of RPLS reported in either Imraldi or Humira treatment group.
- Severity and nature of risk: There were no events of RPLS reported in either Imraldi or Humira treatment group.
- Impact on individual patient: RPLS can significantly impact a patient's quality of life given the severity of this condition, its life-threatening and often fatal nature, and associated co-morbidities.

Risk factors and risk groups: RPLS etiologies include hypertension, eclampsia, and calcineurin inhibitor use. Comorbid conditions include hypertension, renal disease, dialysis dependency, malignancy, and transplantation.[27]

Preventability: There are no preventable measures

Impact on the risk-benefit balance of the product: Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place.

Public health impact: The public health impact is unknown.

Adenocarcinoma of colon in UC patients

Potential mechanisms: The exact mechanism is unknown.

Evidence source(s) and strength of evidence: Imraldi SmPC, Section 4.4 'Special warnings and precautions for use'; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

- Frequency with 95% CI: Not applicable in the Imraldi study
- Seriousness/outcomes: Not applicable in the Imraldi study
- Severity and nature of risk: Not applicable in the Imraldi study
- Impact on individual patient: Adenocarcinoma of colon in UC patients can have direct influence on the patient's quality of life and physical health.

Risk factors and risk groups: Concomitant Primary Sclerosing Cholangitis (PSC), post-inflammatory polyps, family history of colorectal cancer.[28]

Preventability: There are no preventable measures. However, all patients with UC who are at increased risk of colon cancer with multiple risk factors should be screened for dysplasia regularly before treatment and throughout their disease course. The routine evaluation of colonoscopy and biopsies per local recommendation should be followed.[5]

Impact on the risk-benefit balance of the product: Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place.

Public health impact: The potential public health impact is unknown.

SVII.3.2 Presentation of the missing information

Episodic treatment in UC

Evidence source: Not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Population in need of further characterization: Patients with UC

Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD

Evidence source: Not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Population in need of further characterization: Paediatric patients aged from 6 years to less than 18 years with CD

Long-term safety information in the treatment of children aged from 6 years to less than 18 years with UC

Evidence source: Not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Population in need of further characterization: Paediatric patients aged from 6 years to less than 18 years with UC

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII. 1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Serious infections; Tuberculosis (TB); Malignancies; Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barré syndrome [GBS] and optic neuritis); BCG disease following live BCG vaccination in infants with *in utero* exposure to Imraldi
Important potential risks	Progressive multifocal leukoencephalopathy (PML); Reversible posterior leukoencephalopathy syndrome (RPLS); Adenocarcinoma of colon in ulcerative colitis (UC) patients;
Missing information	Episodic treatment in UC; Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD; Long-term safety information in the treatment of children aged from 6 years to less than 18 years with UC

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Other forms of routine pharmacovigilance activities: None

III.2 Additional pharmacovigilance activities

None

III.3 Summary Table of additional Pharmacovigilance activities

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

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
N/A				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A				
Category 3 - Required additional pharmacovigilance activities				
N/A				

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
N/A				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A				

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

Risk Minimisation Plan

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	Routine risk communication: SmPC section 4.3, 4.4, 4.8; PL section 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Signs and symptoms of infections in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: Prescription-only medication
Tuberculosis (TB)	Routine risk communication: SmPC section 4.3, 4.4; PL section 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Screening for tuberculosis in SmPC section 4.4 and PL section 2 Other routine risk minimisation measures beyond the Product Information: Prescription-only medication
Malignancies	Routine risk communication: SmPC section 4.4, 4.8; PL section 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Examination for presence of non-melanoma skin cancer prior to and during treatment in SmPC section 4.4 Language on screening for colonic dysplasia before therapy and at regular intervals during therapy (see also risk of adenocarcinoma of colon in UC) in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: Prescription-only medication
Demyelinating disorders (including MS, GBS, and optic neuritis)	Routine risk communication: SmPC section 4.4, 4.8; PL section 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Neurologic evaluation in patients with non-infectious intermediate uveitis prior to the initiation of the therapy and regularly during the treatment in SmPC section 4.4. Signs and symptoms of demyelinating disease in PL section 2. Other routine risk minimisation measures beyond the Product Information: Prescription-only medication

Safety concern	Routine risk minimisation activities
BCG disease following live BCG vaccination in infants with *in utero* exposure to Imraldi	Routine risk communication: SmPC section 4.4; PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Administration of live vaccines to infants exposed to adalimumab *in utero* is not recommended for 5 months following the mother's last adalimumab injection during pregnancy in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: Prescription-only medication
PML	Routine risk communication: None proposed Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Prescription-only medication
RPLS	Routine risk communication: None proposed Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Prescription-only medication
Adenocarcinoma of colon in UC patients	Routine risk communication: SmPC section 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Regular screening for dysplasia before and throughout the disease course in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: Prescription-only medication
Episodic treatment in UC	Routine risk communication: None proposed Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Prescription-only medication
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD	Routine risk communication: None proposed Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information:

Safety concern	Routine risk minimisation activities
	Prescription-only medication
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with UC	Routine risk communication: None proposed Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Prescription-only medication

V.2. Additional Risk Minimisation Measures

< Patient (including paediatric) Reminder Card >

Objectives:

To provide adequate information to patients to make them aware of the increased risks of the following:

- Serious infections and tuberculosis associated with Imraldi treatment
- BCG disease following live BCG vaccination in infants with *in utero* exposure to Imraldi
- Malignancies (including lymphoma, HSTCL, leukaemia, NMSC, melanoma, merkel cell carcinoma and other malignancies) associated with Imraldi treatment
- Demyelinating disorders (including MS, GBS, and optic neuritis) associated with Imraldi treatment

Rationale for the additional risk minimisation activity:

This particular additional risk minimisation measure for above safety concerns is aligned with that of reference product.

Target audience and planned distribution path:

Patient Reminder Cards are provided to patients receiving Imraldi. This card provides important safety information for patients, including information relating to the above safety concerns.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Not applicable.

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	<Routine risk minimisation measures> SmPC section 4.3, 4.4, 4.8; PL section 2, 4 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Tuberculosis	<Routine risk minimisation measures> SmPC section 4.3, 4.4; PL section 2, 4 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Malignancies	<Routine risk minimisation measures> SmPC section 4.4, 4.8; PL section 2, 4 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Demyelinating disorders (including MS, GBS, and optic neuritis)	<Routine risk minimisation measures> SmPC section 4.4, 4.8; PL section 2, 4 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
BCG disease following live BCG vaccination in infants with *in utero* exposure to Imraldi	<Routine risk minimisation measures> SmPC section 4.4, PL section 2 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
PML	<Routine risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Prescription-only medication <Additional risk minimisation measures> None proposed	<Additional pharmacovigilance activities> None
RPLS	<Routine risk minimisation measures> None proposed Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Adenocarcinoma of colon in UC patients	<Routine risk minimisation measures> SmPC section 4.4 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Episodic treatment in UC	<Routine risk minimisation measures> None proposed Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD	<Routine risk minimisation measures> None proposed Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with UC	<Routine risk minimisation measures> None proposed Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR IMRALDI

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

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

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

I. The medicine and what it is used for

Imraldi is authorised for rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA), enthesitis-related arthritis, ankylosing spondylitis (AS), axial spondyloarthritis without radiographic evidence of AS (nr-axSpA), psoriatic arthritis (PsA), psoriasis (PsO), paediatric plaque PsO, hidradenitis suppurativa (HS), Crohn's disease (CD), paediatric CD, ulcerative colitis (UC), paediatric UC, uveitis and paediatric uveitis (see SmPC for the full indication). It contains adalimumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Imraldi's benefits can be found in Imraldi's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/imraldi

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

Important risks of Imraldi, together with measures to minimise such risks and the proposed studies for learning more about Imraldi'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 the case of Imraldi, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

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

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

II.A List of important risks and missing information

Important risks of Imraldi 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 Imraldi. 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	Serious infections; Tuberculosis (TB); Malignancies; Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barré syndrome [GBS] and optic neuritis); BCG disease following live BCG vaccination in infants with *in utero* exposure to Imraldi
Important potential risks	Progressive multifocal leukoencephalopathy (PML); Reversible posterior leukoencephalopathy syndrome (RPLS); Adenocarcinoma of colon in ulcerative colitis (UC) patients
Missing information	Episodic treatment in UC; Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD; Long-term safety information in the treatment of children aged from 6 years to less than 18 years with UC

II.B Summary of important risks

II.B.1 Important identified risk

Serious infections	
Evidence for linking the risk to the medicine	Study SB5-G31-RA; Imraldi SmPC, Section 4.4 'Special warnings and precautions for use'; referenced scientific publications.

Serious infections	
Risk factors and risk groups	Factors that increase the risk of infection include steroids or other medications that suppress the immune system, such as anti-rejection drugs for a transplanted organ, Human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS), certain types of cancer or other disorders that affect the immune system, implanted medical devices, malnutrition, and increased age.
Risk minimisation measures	<Routine risk minimisation measures> SmPC section 4.3, 4.4, 4.8; PL section 2, 4 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> None See section II.C of this summary for an overview of the post-authorisation development plan.

Tuberculosis	
Evidence for linking the risk to the medicine	Study SB5-G31-RA; Imraldi SmPC, Section 4.4 ‘Special warnings and precautions for use’; referenced scientific publications.
Risk factors and risk groups	Factors that increase the risk of infection include steroids or other medications that suppress the immune system, such as anti-rejection drugs for a transplanted organ, Human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS), certain types of cancer or other disorders that affect the immune system, implanted medical devices, malnutrition, and increased age.
Risk minimisation measures	<Routine risk minimisation measures> SmPC section 4.3, 4.4; PL section 2, 4 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> Registry: Anti-rheumatic Therapies In Sweden (ARTIS), Spanish Registry of Adverse Events of Biological Therapies (BIOBADASER) See section II.C of this summary for an overview of the post-authorisation development plan.

Malignancies	
Evidence for linking the risk to the medicine	Study SB5-G31-RA; Imraldi SmPC, Section 4.4 ‘Special warnings and p recautions for use’; and referenced scientific publications
Risk factors and risk groups	Lymphoma There is an increased background risk for lymphoma and leukaemia in RA patients with long-standing, highly active, inflammatory disease.

Malignancies	
	Studies have shown that patients with RA have an approximately 2-fold increased risk of lymphoma and leukaemia. The increase in lymphoma risk is limited to those RA patients who have long standing and very severe disease. In a prospective study designed to determine the rate of lymphoma among patients with RA, those who developed lymphoma (irrespective of treatment) were significantly older, had more comorbidities, were more likely to be male, had more education, and were more likely to be non-Hispanic whites compared with those that did not develop lymphoma. Factors that increase the risk of HL include age (from 15 to 30 years as well as older than 55 years), a family history of lymphoma, being a male, previous Epstein-Barr virus infection, and a weakened immune system (such as from HIV/AIDS or certain medications after organ transplant). Factors that may increase the risk of NHL include medications that suppress the immune system, infections with certain viruses and bacteria (such as HIV, Epstein-Barr virus, ulcer-causing Helicobacter pylori), and older age (60 years or older) Hepatosplenic T-cell lymphoma (HSTCL) Some of these HSTCLs with adalimumab have occurred in young adult patients on concomitant treatment with azathioprine (AZA) or 6-mercaptopurine (6-MP) used for IBD. The potential risk with the combination of AZA or 6-MP and adalimumab should be carefully considered. Additionally, thiopurine therapy in patients with IBD, combined immunosuppression, age groups from 10 to 35 years, and the male sex are considered to be risk factors of HSTCL. Leukaemia Patients with long-standing, highly active, inflammatory disease, and those with a history of malignancy are at an increased risk of developing leukaemia after treatment with a TNF-antagonist. Caution should also be exercised in considering treatment of patients with increased risk for malignancy due to heavy smoking or chronic obstructive pulmonary disease. Factors with an increased risk of leukaemia include previous chemotherapy and radiation therapy, certain genetic disorders (such as Down syndrome), exposure to certain chemicals (such as benzene), smoking, and a family history of leukaemia. Non-melanoma skin cancer (NMSC) Risk factors of skin cancer include radiation (sunlight or radiation therapy), personal or family history of melanoma, fair skin (having less melanin), certain medical conditions that suppress the immune system, certain medicines (such as some antibiotics, hormones, or antidepressants), and exposure to arsenic at work. In addition, actinic keratosis and HPV infection are also risk factors of skin cancer. Melanoma

Malignancies	
	Among patients considered for TNF-therapy, patients with a history of malignancy, or patients who develop a malignancy during treatment and considering continuation of the treatment. Patients with PsO and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment. . Factors that may increase the risk of melanoma include fair skin (having less melanin), a history of sunburn, a family history of melanoma, excessive ultraviolet (UV) light exposure, many common moles, and a weakened immune system (such as those who have undergone organ transplant). Merkel cell carcinoma (MCC) Factors such as advanced age, immunosuppression (such as organ transplants and HIV), other cancers, and UV light exposure may increase the risk of developing Merkel cell carcinoma.
Risk minimisation measures	<Routine risk minimisation measures> SmPC section 4.4, 4.8; PL section 2 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> Registry: Anti-rheumatic Therapies In Sweden (ARTIS), Spanish Registry of Adverse Events of Biological Therapies (BIOBADASER) See section II.C of this summary for an overview of the post-authorisation development plan.

Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barré syndrome [GBS], and optic neuritis)	
Evidence for linking the risk to the medicine	Study SB5-G31-RA; Imraldi SmPC, Section 4.8 ‘Undesirable effects’ and Section 4.4 ‘Special warnings and precautions for use’; referenced scientific publications.
Risk factors and risk groups	Patients with pre-existing multiple sclerosis (MS) or Guillain-Barré syndrome (GBS) belong to the high-risk group. Additionally, first-degree relatives of patients with MS have an increased propensity for developing MS, with a sibling relative risk ranging between 18 and 36. Factors of increased risk of MS include genetic associations (e.g., HLA-DR2 [HLA-DRB1*15]), ethnic origin (e.g., African American men have lower risk than white men), women, Epstein-Barr virus infection, smoking, and latitude/vitamin D. Factors of increased risk of GBS include men, increased age, viral or bacterial infection (particularly *Campylobacter jejuni* infection), and certain vaccines.

Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barré syndrome [GBS], and optic neuritis)	
Risk minimisation measures	<Routine risk minimisation measures> SmPC section 4.4, 4.8; PL section 2, 4 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> None See section II.C of this summary for an overview of the post-authorisation development plan.

BCG disease following live BCG vaccination in infants with *in utero* exposure to Imraldi	
Evidence for linking the risk to the medicine	Imraldi SmPC, Section 4.6 'Fertility, pregnancy and lactation' and Section 4.4 'Special warnings and precautions for use'
Risk factors and risk groups	Infants who are exposed to Imraldi intrauterine.
Risk minimisation measures	<Routine risk minimisation measures> SmPC section 4.4, PL section 2 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> None See section II.C of this summary for an overview of the post-authorisation development plan.

II.B.2 Important potential risk

Progressive multifocal leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	Referenced scientific publications
Risk factors and risk groups	Immunosuppressive conditions such as HIV/AIDS are the main risk factors of PML. A study conducted by Eng et al. analysed that approximately 41% of the patients with PML were found in the 40 to 49 years age group and the PML patients were predominantly male with a 75% estimate. HIV infection is the basis of approximately 85% of all PML cases. Before the HIV epidemic, more than 60% of PML cases were found in patients with lymphoproliferative disorders. Other conditions that are risk factors of PML are hematologic malignancies, organ transplants, and chronic inflammatory diseases.
Risk minimisation measures	<Routine risk minimisation measures> None proposed

Progressive multifocal leukoencephalopathy (PML)	
	Prescription-only medication <Additional risk minimisation measures> None proposed
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> None See section II.C of this summary for an overview of the post-authorisation development plan.

Reversible posterior leukoencephalopathy syndrome (RPLS)	
Evidence for linking the risk to the medicine	Study SB5-G31-RA; referenced scientific publications.
Risk factors and risk groups	RPLS etiologies include hypertension, eclampsia, and calcineurin inhibitor use. Comorbid conditions include hypertension, renal disease, dialysis dependency, malignancy, and transplantation.
Risk minimisation measures	<Routine risk minimisation measures> None proposed Prescription-only medication <Additional risk minimisation measures> None proposed
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> None See section II.C of this summary for an overview of the post-authorisation development plan.

Adenocarcinoma of colon in ulcerative colitis (UC) patients	
Evidence for linking the risk to the medicine	Imraldi SmPC, Section 4.4 ‘Special warnings and precautions for use’; referenced scientific publications.
Risk factors and risk groups	Concomitant Primary Sclerosing Cholangitis (PSC), post-inflammatory polyps, family history of colorectal cancer.
Risk minimisation measures	<Routine risk minimisation measures> SmPC section 4.4 Prescription-only medication <Additional risk minimisation measures> None proposed
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> None See section II.C of this summary for an overview of the post-authorisation development plan.

II.B.3 Missing information

Episodic treatment in UC	
Risk minimisation measures	<Routine risk minimisation measures> None proposed Prescription-only medication <Additional risk minimisation measures> None proposed
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> Registry: ARTIS, BIOBADASER See section II.C of this summary for an overview of the post-authorisation development plan.

Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD	
Risk minimisation measures	<Routine risk minimisation measures> None proposed Prescription-only medication <Additional risk minimisation measures> None proposed
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> None See section II.C of this summary for an overview of the post-authorisation development plan.

Long-term safety information in the treatment of children aged from 6 years to less than 18 years with UC	
Risk minimisation measures	<Routine risk minimisation measures> None proposed Prescription-only medication <Additional risk minimisation measures> None proposed
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> None See section II.C of this summary for an overview of the post-authorisation development plan.

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 Imraldi.

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

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
N/A				

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities

Approved key messages of the additional risk minimisation measures

< Patient Reminder Card>

- A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Imraldi
- Information on date of therapy initiation and current administrations
- A warning message for patients to show the card to any doctor or health care professional they see
- Precautions on the safety concerns, including infections, tuberculosis, cancer, nervous system problems, and vaccinations before treatment initiation
- Signs or symptoms of the safety concerns and when to seek attention from a healthcare professional
- Contact details of the Imraldi prescriber
- Type, date and result of last TB screening(s)