EU Risk Management Plan

for

YUFLYMA®

(CT-P17, Biosimilar adalimumab)

RMP version to be assessed as part of this application:	
RMP version number:	4.0
Data lock point for this RMP:	15 July 2025
Date of final sign off:	18 December 2025
Rationale for submitting an updated RMP:	The Risk Management Plan (RMP) has been updated to harmonise the safety concerns in line with the reference product, Humira.
Summary of significant changes in this RMP:	Part II : Safety specification • The missing information "Long-term safety information in the treatment of children with uveitis" has been removed in order to align with reference product, Humira. • The missing information "Episodic treatment in Ps, UC and JIA" has been reclassified to "Episodic treatment in UC" in order to align with reference product, Humira.
Other RMP versions under evaluation: Not applicable	
RMP version number:	-
Submitted on:	-
Procedure number:	-
Details of the currently approved RMP:	
Version number:	4.0
Approved with procedure:	EMA/R/0000295845
Date of approval (opinion date):	11 December 2025

QPPV name: Oliver Wiedemann

QPPV signature: *The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.*

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Abbreviations

Term	Explanation
6-MP	6-Mercaptopurine
ADR	Adverse Drug Reaction
AE	Adverse Event
AI	Auto-injector
AIDS	Acquired Immunodeficiency Syndrome
ARD	Autoimmune Rheumatic Disease
AS	Ankylosing Spondylitis
AZA	Azathioprine
BBB	Blood-brain Barrier
BCG	Bacillus Calmette–Guérin
BP	Blood Pressure
CD	Crohn's Disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CNS	Central Nervous System
DMARD	Disease-modifying Anti-rheumatic Drug
ECG	Electrocardiogram
EU	European Union
GBS	Guillain Barré Syndrome
GI	Gastrointestinal
AGVP	Good Pharmacovigilance Practices
HBV	Hepatitis B Virus
HIV	Human Immunodeficiency Virus
HS	Hidradenitis Suppurativa
ICH	International Council for Harmonisation
Ig	Immunoglobulin
JC	John Cunningham
JIA	Juvenile Idiopathic Arthritis
mAb	Monoclonal Antibody

MS	Multiple Sclerosis
MTX	Methotrexate
NK	Natural killer
NSAID	Nonsteroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
ON	Optic Neuritis
OR	Odds Ratio
PD	Pharmacodynamics
PFS	Pre-filled Syringe
PK	Pharmacokinetics
PL	Package Leaflet
PML	Progressive Multifocal Leukoencephalopathy
Ps	Psoriasis
PsA	Psoriatic Arthritis
PUVA	Psoralen and Ultraviolet A
RA	Rheumatoid Arthritis
RMP	Risk Management Plan
RPLS	Reversible Progressive Leukoencephalopathy Syndrome
RRMS	Relapsing-remitting Phase of Multiple Sclerosis
SLE	Systemic Lupus Erythematosus
SmPC	Summary of Product Characteristics
SpA	Spondyloarthritis
TB	Tuberculosis
TNF	Tumour Necrosis Factor
UC	Ulcerative Colitis
UV	Uveitis

Part I: Product(s) Overview

Table 1 Part I.1 - Product(s) Overview

Active substance(s) **(INN or common name)**	Adalimumab
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors (L04AB04)
Marketing Authorisation Applicant	Celltrion Healthcare Hungary Kft.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Yuflyma®
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Adalimumab is a human immunoglobulin (Ig) G1 monoclonal antibody (mAb) directed against tumour necrosis factor-alpha (TNF-α).
	Summary of mode of action: Adalimumab binds specifically to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC50 of 0.1-0.2 nM).
	Important information about its composition: Adalimumab is a recombinant human monoclonal antibody produced in Chinese Hamster Ovary cells.
Hyperlink to the Product Information	CTD Module 1.3.1
Indication(s) in the EEA	**Current:** <u>Rheumatoid arthritis (40mg, 80mg)</u> Yuflyma in combination with methotrexate, is indicated for: • the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-

	modifying anti-rheumatic drugs including methotrexate has been inadequate. • the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. Yuflyma can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Adalimumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate. <u>Juvenile idiopathic arthritis (20mg, 40mg)</u> *Polyarticular juvenile idiopathic arthritis* Yuflyma in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Yuflyma can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Adalimumab has not been studied in patients aged less than 2 years. *Enthesitis-related arthritis:* Yuflyma is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy. <u>Axial spondyloarthritis (40mg)</u> *Ankylosing spondylitis (AS)* Yuflyma is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy. *Axial spondyloarthritis without radiographic evidence of AS* Yuflyma is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated C-Reactive Protein and/or magnetic resonance imaging, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory

	drugs (NSAIDs). Psoriatic arthritis (40mg) Yuflyma is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Adalimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function. Psoriasis (40mg, 80mg) Yuflyma is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy. Paediatric plaque psoriasis (20mg, 40mg) Yuflyma is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies. Hidradenitis suppurativa (HS) (40mg, 80mg) Yuflyma is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy. Crohn's disease (40mg, 80mg) Yuflyma is indicated for treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. Paediatric Crohn's disease (20mg, 40mg, 80mg) Yuflyma is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies. Ulcerative colitis (40mg, 80mg) Yuflyma is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an

	inadequate response to conventional therapy including corticosteroids and 6-Mercaptopurine (6-MP) or Azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies. Paediatric Ulcerative Colitis (40mg, 80mg) Yuflyma is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including corticosteroids and/or 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies. Uveitis (40mg, 80mg) Yuflyma is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate. Paediatric Uveitis (20mg, 40mg, 80mg) Yuflyma is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

Dosage in the EEA	**Current:** *Rheumatoid arthritis* The recommended dose of Yuflyma for adult patients with rheumatoid arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection. In monotherapy, some patients who experience a decrease in their response to Yuflyma 40 mg every other week may benefit from an increase in dosage to 40 mg adalimumab every week or 80 mg every other week. *Ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS and psoriatic arthritis* The recommended dose of Yuflyma 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. *Psoriasis* The recommended dose of Yuflyma 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. Yuflyma 40 mg solution for injection in pre-filled syringe and/or pre-filled pen is available for the maintenance dose. Beyond 16 weeks, patients with inadequate response to Yuflyma 40 mg every other week may benefit from an increase in dosage to 40 mg every week or 80 mg every other week. *Hidradenitis suppurativa* The recommended Yuflyma 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 or as two 80 mg injections in one day or as one 80 mg injection 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). *Crohn's disease* The recommended Yuflyma 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 or as two 80 mg injections in one day or as one 80 mg injection per day for two consecutive days), followed by 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.

Ulcerative colitis

The recommended Yuflyma 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 or as two 80 mg injections in one day or as one 80 mg injection per day for two consecutive days) and 80 mg at Week 2 (given as one 80mg injection or two 40 mg injections in one day). After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection.

Uveitis

The recommended dose of Yuflyma 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. Yuflyma 40 mg solution for injection in pre-filled syringe and/or pre-filled pen is available for the maintenance dose.

Special populations

Polyarticular juvenile idiopathic arthritis from 2 years of age

The recommended dose of Yuflyma for patients with polyarticular juvenile idiopathic arthritis from 2 years of age is based on body weight.

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

Enthesitis-related arthritis

The recommended dose of Yuflyma for patients with enthesitis-related arthritis from 6 years of age is based on body weight.

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

≥ 30 kg	40 mg every other week

Paediatric plaque psoriasis

The recommended Yuflyma 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 Yuflyma dose is 80 mg at Week 0 followed by 40 mg every other week starting at Week 1 via subcutaneous injection.

Paediatric Crohn's disease

The recommended dose of Yuflyma 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

Paediatric Uveitis

The recommended dose of Yuflyma for paediatric patients with uveitis from 2 years of age is based on body weight.

Patient Weight	**Dosing Regimen**
< 30 kg	20 mg every other week in combination with methotrexate
≥ 30 kg	40 mg every other week in combination with methotrexate

When Yuflyma therapy is initiated, a loading dose of 40 mg for patients < 30 kg or 80 mg for patients ≥ 30 kg may be administered one week prior to the start of maintenance therapy.

Paediatric Ulcerative colitis

The recommended dose of Yuflyma 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 or one 80 mg injection in one day) and • 40 mg at Week 2 (given as one 40 mg 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 days or two 80 mg injections in one day or one 80 mg injection per day for two consecutive days) and • 80 mg at Week 2 (given as two 40 mg injections in one day)	• 80 mg every other week

Pharmaceutical form(s) and strengths

Current:

Yuflyma 20 mg solution for subcutaneous injection.

Each 0.2 ml single-dose pre-filled syringe contains 20 mg of adalimumab.

Yuflyma 40 mg solution for subcutaneous injection.

Each 0.4 ml single-dose pre-filled syringe/pre-filled pen contains 40 mg of adalimumab.

Yuflyma 80 mg solution for subcutaneous injection.

	Each 0.8 ml single-dose pre-filled syringe/pre-filled pen contains 80 mg of adalimumab.
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety Specification

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

According to the Guideline on Good Pharmacovigilance Practices (GVP) Module V (EMA/838713/2011 Rev. 2), this part of the Risk Management Plan (RMP) is not required for biosimilar medicinal products.

Part II: Module SII - Non-Clinical Part of the Safety Specification

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

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity	
Repeat-Dose Toxicity *Monkey (Cynomolgus monkey):* *3 animals/sex/group, doses of CT-P17 and Humira® at 0, 32 and 157 mg/kg s.c. on days 1, 8, 15 and 22 (Study No. 1878-030).* Assessment of toxicity was based on mortality, clinical observations, body weight, body temperature, and food consumption; ophthalmoscopy and electrocardiogram (ECG) examinations; and clinical pathology (haematology, coagulation, clinical chemistry, urinalysis and immunophenotyping), and anatomic pathology (macroscopic observations, organ weight and microscopic observations). All animals survived to the scheduled necropsy. No CT-P17- or Humira®-related effects were noted in clinical observations, food consumption, body weights, ophthalmoscopic findings, qualitative or quantitative ECG parameters, clinical pathology endpoints (haematology, coagulation, clinical chemistry, urinalysis or immunophenotyping), macroscopic observations or organ weights. Test article-related microscopic findings included minimal to moderate depletion of the germinal centers in the spleen and mandibular and/or mesenteric lymph nodes. Animals treated with Humira® had a higher incidence of germinal center depletion in the spleen, compared to animals treated with CT-P17 and concurrent study control animals. This finding was not dose dependent; however, females were affected at a greater frequency compared to males. The incidence and severity (minimal) of germinal center depletion in the lymph nodes were similar between animals treated with CT-P17 and Humira®. Minimal lymphoid depletion of the thymic cortex was present in all males treated with 157 mg/kg CT-P17 and 32 mg/kg or 157 mg/kg Humira® and in one female treated with 32 mg/kg Humira®. In the males, the incidence and severity were identical across affected groups of animals, and the change was minimal. There was no dose response present in females, as there was only a single animal affected. Due to a single incidence or lack of dose response, all other microscopic findings were considered incidental or common background lesions in monkeys.	Humira® has been used safely in the clinic since 1998. During the repeat-dose toxicity studies, no toxicologically relevant differences were noted in animals treated with CT-P17 or Humira®. Therefore, relevance to human usage was not found.

Key Safety findings (from non-clinical studies)	Relevance to human usage
In conclusion, once weekly subcutaneous administration of 32 or 157 mg/kg CT-P17 or 32 or 157 mg/kg Humira® was well tolerated. The only CT-P17- or Humira®-related observations were microscopic findings in the mandibular and/or mesenteric lymph nodes, spleens, or thymus. No toxicologically relevant differences were noted in animals treated with CT-P17 or Humira®.	
Reproductive and Developmental Toxicity According to EMA guidelines: Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1); Similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010); and International Council for Harmonisation (ICH) S6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH 2011), reproduction toxicology studies are not required for similar biological medicinal products unless indicated by results of repeat-dose studies. In compliance with the guidelines, no reproductive and developmental toxicity studies have been conducted with CT-P17. Tissues from reproductive organs were evaluated in terms of macroscopic and microscopic histopathology in the 4 weeks repeat-dose toxicity study (Study No. 1878-030). No treatment related histopathology changes were noted in reproductive organs.	None
Genotoxicity/Carcinogenicity No genotoxicity or carcinogenicity studies have been conducted for CT-P17 in line with the ICH S6 (R1) Guideline (ICH 2011) which states that such studies are generally inappropriate for biotechnology-derived products because large proteins, such as monoclonal antibodies, would not be expected to pass through cell membranes and interact directly with DNA or other chromosomal material. In EMA 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), it is also advised that carcinogenicity is not required for similar biological medicinal products, unless indicated by results of repeat-dose studies.	None

Key Safety findings (from non-clinical studies)	Relevance to human usage
Safety pharmacology	
Cardiotoxicity No specific safety pharmacology studies were performed. Safety end-points were incorporated into the monkey repeat-dose toxicity study (Study No. 1878-030), and there was no evidence of cardiotoxicity in the study.	None
General Safety Pharmacology No specific safety pharmacology studies were performed. Safety end-points were incorporated into the monkey repeat-dose toxicity study (Study No. 1878-030). This approach is compatible with EMA Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010), which states that safety pharmacology studies are not routinely required.	None
Other toxicity-related information or data	
Mechanisms for Drug Interactions On the basis of the specificity of adalimumab, the extensive clinical experience with the reference product and the lack of documented drug-drug interactions, no non-clinical studies pertinent to drug interaction have been conducted.	None

Part II: Module SIII - Clinical Trial Exposure

Yuflyma (CT-P17) is developed as a biosimilar medicinal product to the reference product, Humira® (adalimumab). Humira® was approved in the European Union (EU) for subcutaneous infusion available as a vial, pre-filled syringe (PFS) or pre-filled pen while Yuflyma has been developed for subcutaneous infusion via PFS or pre-filled pen which is also referred to as auto-injector (AI).

Yuflyma is developed for the same indications for which Humira® is authorised in the EU, namely Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA), Axial Spondyloarthritis (axial SpA), Psoriatic Arthritis (PsA), Psoriasis (Ps), paediatric plaque Ps, Hidradenitis Suppurativa (HS), Crohn's Disease (CD), paediatric CD, Ulcerative Colitis (UC), paediatric UC, Uveitis (UV) and paediatric UV used alone or in combination with non-biologic disease-modifying anti-rheumatic drugs (DMARDs) representing prior standard of care for these indications.

There are five studies in clinical development programme with CT-P17, comprising three studies to compare biosimilarity between CT-P17 and Humira® (Studies CT-P17 1.1, CT-P17 1.2 and CT-P17 3.1) and two studies for evaluation of AI presentation (Studies CT-P17 1.3 and CT-P17 3.2).

As of the data lock point, all of clinical studies with CT-P17 below have been completed.

- Study CT-P17 1.1 (Pharmacokinetics (PK) study for biosimilarity): A phase 1, randomised, single-dose study to evaluate PK, safety, and immunogenicity of CT-P17 PFS, EU-approved Humira® PFS and US-licensed Humira® PFS in healthy male and female subjects.
- Study CT-P17 1.2 (pilot study): A pilot phase 1, randomised, single-dose study to evaluate the safety, PK, and immunogenicity of CT-P17 PFS and EU-approved Humira® PFS in healthy male subjects.
- Study CT-P17 1.3 (PK study between AI and PFS): A phase 1, randomised, open-label, single-dose study to evaluate PK, safety, and immunogenicity of CT-P17 subcutaneous administration via AI versus PFS in healthy male and female subjects.
- Study CT-P17 3.1 (confirmatory efficacy and safety study): A phase 3, randomised, active-controlled study to evaluate efficacy, PK, pharmacodynamics (PD), usability, safety, and immunogenicity of CT-P17 PFS and EU-approved Humira® PFS when co-administered with methotrexate (MTX) in patients with moderate to severe active RA.
- Study CT-P17 3.2 (AI usability study): A phase 3, open-label, multiple-dose study to evaluate usability, safety, and efficacy of CT-P17 AI in patients with moderate to severe active RA.

A total of 518 healthy subjects were involved in the completed clinical studies of CT-P17 (Studies CT-P17 1.1, CT-P17 1.2, and CT-P17 1.3). Of those, 204, 93 and 221 subjects received CT-P17 via PFS, CT-P17 via AI and Humira® via PFS, respectively.

The clinical safety data for CT-P17 are available from one double-blinded study with RA patients, Study CT-P17 3.1 and one open-label study with RA patients, Study CT-P17 3.2. A total of 538 patients with RA were exposed to at least 1 dose of CT-P17 and 324 to Humira®, among which 152 patients who received Humira® during Treatment Period I up to Week 24 were switched to treatment with CT-P17 during Treatment Period II up to Week 48 in Study CT-P17 3.1. The following tables summarise patients' exposure included in Study CT-P17 3.1 and Study CT-P17 3.2.

Table 2 SIII.1: Duration of Exposure

INDICATION: Rheumatoid Arthritis								
Treatment	**CT-P17 40 mg**						**Adalimumab Reference Product 40 mg**	
	CT-P17 Total		**CT-P17 Only**		**Switched from reference product***			
Duration of exposure	**Subjects (n)**	**Subject-time (days)**	**Subjects (n)**	**Subject-time (days)**	**Subjects (n)**	**Subject-time (days)**	**Subjects (n)**	**Subject-time (days)**
≤ 6 months	231	34420	79	11413	152	23007	110	17854
> 6 months - ≤ 12 months	305	101526	305	101526	0	0	213	62619
> 12 months - ≤ 18 months	2	739	2	739	0	0	1	368
Total	538	136685	386	113678	152	23007	324	80841

Source: Study CT-P17 3.1 and Study CT-P17 3.2

Subject time (days) = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1)

1 month = 30.4375 days

* Subjects switched to CT-P17 from reference product after completion of Week 24 Treatment in Study CT-P17 3.1.

Table 3 SIII.2: Age group and Gender

INDICATION: Rheumatoid Arthritis																
Treatment	**CT-P17 40 mg**												**Adalimumab Reference Product 40 mg**			
	CT-P17 Total				**CT-P17 Only**				**Switched from reference product***							
	Subjects (n)		**Subject-time (days)**		**Subjects (n)**		**Subject-time (days)**		**Subjects (n)**		**Subject-time (days)**		**Subjects (n)**		**Subject-time (days)**	
Age Group (years)	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
18 - 40	18	78	4284	19694	13	57	3506	16455	5	21	778	3239	10	50	2615	13171
41 - 50	22	104	5501	27387	18	76	4876	23336	4	28	625	4051	7	60	1698	15495
51 - 64	67	176	18299	41898	52	109	15943	31791	15	67	2356	10107	33	122	8841	27955
≥ 65	16	57	3750	15872	12	49	3133	14638	4	8	617	1234	9	33	2407	8659
Total	123	415	31834	104851	95	291	27458	86220	28	124	4376	18631	59	265	15561	65280

Source: Study CT-P17 3.1 and Study CT-P17 3.2

Subject time (days) = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1)

* Subjects switched to CT-P17 from reference product after completion of Week 24 Treatment in Study CT-P17 3.1.

Table 4 SIII.3: Dose

INDICATION: Rheumatoid Arthritis								
Treatment	CT-P17 40 mg						Adalimumab Reference Product 40 mg	
	CT-P17 Total		CT-P17 Only		Switched from reference product*			
Number of Treatment Administration	Subjects (n)	Subject-time (days)	Subjects (n)	Subject-time (days)	Subjects (n)	Subject-time (days)	Subjects (n)	Subject-time (days)
1	5	5	3	3	2	2	3	3
2	0	0	0	0	0	0	0	0
3	4	114	3	88	1	26	1	29
4	1	45	1	45	0	0	3	135
5	3	199	1	55	2	144	1	69
6	2	142	2	142	0	0	2	140
7	3	270	2	178	1	92	3	290
8	3	311	3	311	0	0	2	195
9	4	462	3	349	1	113	3	419
10	4	592	1	127	3	465	1	126
11	9	1375	3	458	6	917	1	182
12	141	22109	5	861	136	21248	7	1264
13	56	9534	56	9534	0	0	145	26604
14	1	183	1	183	0	0	0	0
15	1	211	1	211	0	0	0	0
16	3	646	3	646	0	0	0	0
17	2	454	2	454	0	0	1	224
18	3	772	3	772	0	0	0	0
19	1	289	1	289	0	0	1	287
20	0	0	0	0	0	0	2	561
21	1	280	1	280	0	0	0	0
22	1	293	1	293	0	0	2	645
23	4	1375	4	1375	0	0	3	1045
24	20	6801	20	6801	0	0	12	4101
25	266	90223	266	90223	0	0	131	44522
Total	538	136685	386	113678	152	23007	324	80841
Total Cumulative Dose (mg) Mean	753.7	-	868.2	-	462.9	-	721.1	-
Total Cumulative Dose (mg) Median	960.0	-	1000.0	-	480.0	-	520.0	-

Total Cumulative Dose (mg) Min	40	-	40	-	40	-	40	-
Total Cumulative Dose (mg) Max	1000	-	1000	-	480	-	1000	-

Source: Study CT-P17 3.1 and Study CT-P17 3.2
Subject time (days) = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1)
* Subjects switched to CT-P17 from reference product after completion of Week 24 Treatment in Study CT-P17 3.1.

Table 5 SIII.4: Ethnic Origin

INDICATION: Rheumatoid Arthritis								
Treatment	**CT-P17 40 mg**						**Adalimumab Reference Product 40 mg**	
	CT-P17 Total		**CT-P17 Only**		**Switched from reference product***			
Ethnic Origin	**Subjects (n)**	**Subject-time (days)**	**Subjects (n)**	**Subject-time (days)**	**Subjects (n)**	**Subject-time (days)**	**Subjects (n)**	**Subject-time (days)**
Not allowed by investigator country regulations	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0
White	502	127109	361	105746	141	21363	298	73663
Black or African American	0	0	0	0	0	0	0	0
Other	36	9576	25	7932	11	1644	26	7178
Total	538	136685	386	113678	152	23007	324	80841

Source: Study CT-P17 3.1 and Study CT-P17 3.2
Subject time (days) = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1)
* Subjects switched to CT-P17 from reference product after completion of Week 24 Treatment in Study CT-P17 3.1.

Table 6 SIII.5: Special Population

INDICATION: Rheumatoid Arthritis								
Treatment	**CT-P17 40 mg**							
	CT-P17 Total		**CT-P17 Only**		**Switched from reference product***		**Adalimumab Reference Product 40 mg**	
Special Population	**Subjects (n)**	**Subject-time (days)**	**Subjects (n)**	**Subject-time (days)**	**Subjects (n)**	**Subject-time (days)**	**Subjects (n)**	**Subject-time (days)**
Children [1]	0	0	0	0	0	0	0	0
Pregnant women [1]	0	0	0	0	0	0	0	0
Breastfeeding women [1]	0	0	0	0	0	0	0	0
Renal impairment [1]	0	0	0	0	0	0	0	0
Hepatic impairment [1]	0	0	0	0	0	0	0	0
Cardiac impairment [2]	5	1367	5	1367	0	0	1	337
FcγR IIa sub-population; Het Pos AG [3]	195	53298	140	44717	55	8581	125	31515
FcγR IIa sub-population; Hom Pos GG [3]	57	14757	38	11786	19	2971	43	11572
FcγR IIa sub-population; Wildtype AA [3]	130	33164	82	26087	48	7077	96	22920
FcγR IIIa sub-population; Het Pos AC [3]	179	47986	126	39928	53	8058	112	27122
FcγR IIIa sub-population; Hom Pos CC [3]	41	11898	32	10570	9	1328	26	7135
FcγR IIIa sub-population; Wildtype AA [3]	162	41335	102	32092	60	9243	126	31750

Source: Study CT-P17 3.1 and Study CT-P17 3.2

Subject time (days) = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1)

[1] Patients who meet this definition were ineligible for all studies according to the Inclusion/ Exclusion criteria.

[2] Patients are defined as those patients who satisfy at least one of the following criteria:
1. Patients whose screening ECG test was reported as abnormal and clinically significant.
2. Patients who had a medical history of cardiac failure, cardiac failure chronic or cardiac failure congestive.

[3] FcγR subpyting was performed only in Study CT-P17 3.1.

* Subjects switched to CT-P17 from reference product after completion of Week 24 Treatment in Study CT-P17 3.1.

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

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

Previously received investigational or licensed product, biologic or targeted synthetic disease-modifying anti-rheumatic drugs (DMARDs) (e.g., tofacitinib, baricitinib) for the treatment of RA and/or tumour necrosis factor (TNF) α inhibitor for any purposes.

Reason for exclusion: The previous use of investigational or licensed product; biologic or targeted synthetic DMARDs (e.g., tofacitinib, baricitinib) and/or TNF-α inhibitors were prohibited or required a washout period as these could confound the interpretation of efficacy study endpoints.

Is it considered to be included as missing information?: No

Rationale: Clinical experience and post-authorisation exposure of reference product Humira® indicate that adalimumab may also be administered safely to subjects previously exposed to above medicinal products, with appropriate monitoring.

Allergy to any of the excipients of CT-P17 or any other murine and human proteins, or hypersensitivity to immunoglobulin products.

Reason for exclusion: Patients with a history of allergy to any of the excipients of CT-P17 or any other murine and human proteins, or patients with a hypersensitivity to immunoglobulin products were excluded from the clinical development programme for safety reasons. Patients with a known allergy would be at a higher risk of subsequent serious systemic hypersensitivity reactions with re-exposure.

Is it considered to be included as missing information?: No

Rationale: Similar to all medicinal products, patients with a known hypersensitivity to the active substance (adalimumab) or to any of the excipients of Yuflyma are contraindicated and therefore it is unlikely that Yuflyma will be used in this population.

Current or past history of tuberculosis (TB) or other serious infections; or recent exposure to persons with active TB, or a positive result to the screening test for latent TB defined as a positive result of interferon-γ release assay with a negative examination of chest X-ray.

Reason for exclusion: Anti-TNF-α agents have been associated with an increased risk of serious infections including TB, bacterial infections, including sepsis and pneumonia, invasive fungal, viral, and other opportunistic infections; these infections are a class effect of anti-TNF-α agents. Risk of development of TB or other serious infections during the study would be increased leading to increased risk of dropout from the study, therefore patients with TB or other serious infections were excluded from the clinical development programme.

Is it considered to be included as missing information?: No

Rationale: The available evidence from the use of adalimumab is already sufficient to contraindicate its use in the patients with TB or other severe infections such as sepsis, and opportunistic infections. Serious infections have been included in the RMP as an important identified risk.

New York Heart Association (NYHA) Class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina or clinically significant electrocardiogram [ECG] abnormalities), or myocardial infarction.

Reason for exclusion: Adalimumab is contraindicated in subjects with NYHA Class III or IV heart failure, therefore, these patients were excluded from the clinical development programme.

Is it considered to be included as missing information?: No

Rationale: The available evidence from the use of adalimumab is already sufficient to contraindicate its use in the patients with moderate to severe heart failure (NYHA class III/IV). Cases of worsening congestive heart failure have also been reported in patients receiving the reference product Humira®. The Humira® product information advises that it should be used with caution in patients with mild heart failure (NYHA class I/II) and that treatment must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Received or plans to receive live or live-attenuated vaccine.

Reason for exclusion: Live vaccines should not be administered during treatment with TNF-inhibitors because of the risk of infection with live vaccine.

Is it considered to be included as missing information?: No

Rationale: There is sufficient evidence that immunosuppression due to inhibition of TNF may increase the risk of complications associated with live vaccines.

Pregnant or breast-feeding, or planning to become pregnant or breast-feed.

Reason for exclusion: The use of adalimumab is not contraindicated during pregnancy and breast-feeding, however, the effect of TNF inhibition on the immune system of the developing foetus is not known and use is therefore not recommended if there are more suitable alternatives.

Is it considered to be included as missing information?: No

Rationale: Data, from a large number (approximately 2,100) of prospectively collected pregnancies exposed to Humira® resulting in live birth with known outcomes, including more than 1,500 exposed during the first trimester, do not indicate an increase in the rate of malformation in the new-born.

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

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

Adverse drug reactions (ADRs) with a frequency greater than 1 in 179 subjects with RA may be detected with a data set of this size.

ADRs which require an exposure of longer than 12 months to develop in subjects with RA would not be expected to be detected in the safety data set.

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

Table 7 SIV.1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Not included in the clinical development program
• Patients with renal impairment	Not included in the clinical development program
• Patients with cardiovascular impairment	Five subjects with cardiac impairment (defined as an abnormal electrocardiogram at screening, or a history of cardiac failure) were treated with CT-P17 for RA in clinical studies, and one with the reference product (Table 6)
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	The majority of subjects in RA data set exposed to CT-P17 in Study CT-P17 3.1 and Study CT-P17 3.2 were White (n=502). No Black or Asian subjects with RA have been exposed to CT-P17 (Table 5).
Subpopulations carrying relevant genetic polymorphisms	FcγRIIa and FcγRIIIa receptor subtyping were performed on 382 subjects in the RA data set exposed to CT-P17 in Study CT-P17 3.1. In regard to FcγRIIa subtypes, the majority of subjects (n=195) treated with CT-P17 were with Het Pos AG subtype, followed by sub-population with Wildtype AA (n=130). And the rest of subjects had Hom Pos GG (n=57). Similarly, among subjects who had FcγRIIIa results, the majority of subjects (n=179) treated with CT-P17 were with Het Pos AC subtype, followed by sub-population with Wildtype AA (n=162). And the rest of subjects had Hom Pos CC (n=41). (Table 6).

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

The first granted marketing authorisation of Yuflyma was in EU on 11 February 2021.

SV.1.1 Method used to calculate exposure

The estimate of patient exposure during the cumulative period since IBD was calculated based on the sales volumes of active ingredient in mg and the Defined Daily Dose (DDD) provided by the World Health Organisation (WHO) Collaborating Centre for Drug Statistics Methodology in Oslo, which is 2.9 mg for adalimumab.

Patient exposure (patient-days) = Number of dosage forms sold x dosage form strength in mg / DDD in mg

Patient exposure (patient-years) = Patient exposure (patient-days)/365.25

SV.1.2 Exposure

Table 8 SV.1: Cumulative Patient Exposure from Marketing Experience[#]

	Sales of finished product (20mg)	Sales of finished product (40mg)	Sales of finished product (80mg)	Patient-days	Patient-years
Total	6,092	5,240,136	333,539	1,924,058	5,268
[#]The cumulative patient exposure is based on sales data from 11 Feb 2021 to 15 Jul 2025.					

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

Potential for misuse for illegal purposes

Based on the given mechanism of action of the adalimumab and its indications, the potential for misuse or abuse for illegal purposes is considered negligible.

Potential for risks associated with device component of the product

Yuflyma (CT-P17) is administered subcutaneously through an injection device, PFS or AI. In clinical trials of CT-P17 with RA patients, which consist of Study CT-P17 3.1 with PFS and CT-P17 3.2 with AI, there were only a total of 3 occurrences (0.38 % over total used AIs) of AI device failure all leading to no dose injection, and no device error was reported with PFS. Each clinical trial in which the usability of PFS and AI was evaluated respectively, also presented high usability of both PFS and AI. There are currently no post-marketing experiences with Yuflyma as it has not been marketed in any country. Based on currently available information, no particular device-related risk has been identified.

Once marketing authorisation of Yuflyma is granted, data related to device function, usability, and medication errors due to device component along with relevant AEs will be consistently collected and reviewed through routine pharmacovigilance activities and monitoring of product complaints, in order to identify any risks related to the use of medical device. Medication errors and AEs associated with device will be databased in Celltrion's global safety database.

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

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

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

Not known.

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

Not known.

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

Not known.

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

Not known.

Other reasons for considering the risks not important:

Yuflyma is a biosimilar medicinal product to the reference product, Humira®. Yuflyma and its reference product Humira® contain the same active substance, adalimumab. Yuflyma has been shown to have a comparable safety and efficacy profile to Humira® in clinical studies. The two products are therapeutically equivalent. The risks attached to the two products are therefore also considered to be equivalent in all respects. Many of the risks known to be associated with Humira® have not been observed in the clinical development studies conducted with Yuflyma. The reasons for not including an identified or potential risk in the list of safety concerns for Yuflyma are based solely on experience gathered from Humira®.

The following risks are currently labelled in the Humira® product information and are not important safety concerns for either Humira® or Yuflyma:

Leukopenia (including neutropenia and agranulocytosis), Anaemia, Leucocytosis, Thrombocytopenia, Idiopathic thrombocytopenic purpura, Pancytopenia, Hypersensitivity, Allergies (including seasonal allergy), Sarcoidosis, Vasculitis, Anaphylaxis, Lipids increased, Hypokalaemia, Uric acid increased, Blood sodium abnormal, Hypocalcaemia, Hyperglycaemia, Hypophosphatemia, Dehydration, Mood alterations (including depression), Anxiety, Insomnia, Headache, Paraesthesias (including hypoesthesia), Migraine, Nerve root compression, Cerebrovascular accident, Tremor, Neuropathy, Visual impairment, Conjunctivitis, Blepharitis,

Eye swelling, Diplopia, Vertigo, Deafness, tinnitus, Tachycardia, Myocardial infarction, Arrhythmia, Congestive heart failure, Cardiac arrest, Hypertension, Flushing, Haematoma, Aortic aneurysm, Vascular arterial occlusion, Thrombophlebitis, Asthma, Dyspnoea, Cough, Pulmonary embolism, Interstitial lung disease, Chronic obstructive Pulmonary disease, Pneumonitis, Pleural effusion, Pulmonary fibrosis, Abdominal pain, Nausea and vomiting, Gastrointestinal (GI) haemorrhage, Dyspepsia, Gastroesophageal reflux disease, Sicca syndrome, Pancreatitis, Dysphagia, Face oedema, Intestinal perforation, Elevated liver enzymes, Cholecystitis and cholelithiasis, Hepatic steatosis, Bilirubin increased, Hepatitis, Reactivation of hepatitis B, Autoimmune hepatitis, Liver failure, Rash (including exfoliative rash), Worsening or new onset of psoriasis (including palmoplantar pustular psoriasis), Urticaria, Bruising (including purpura), Dermatitis (including eczema), Onychoclasis, Hyperhidrosis, Alopecia, Pruritus, Night sweats, Scar, Erythema multiforme, Stevens-Johnson syndrome, Angioedema, Cutaneous vasculitis, lichenoid skin reaction, Worsening of symptoms of dermatomyositis, Musculoskeletal pain, Muscle spasms (including blood creatine phosphokinase increased), Rhabdomyolysis, Systemic lupus erythematosus, Lupus-like syndrome, Renal impairment, Haematuria, Nocturia, Erectile dysfunction, Injection site reaction (including injection site erythema), Chest pain, Oedema, Pyrexia, Inflammation, Coagulation and bleeding disorders (including activated partial thromboplastin time prolonged), Autoantibody test positive (including double stranded DNA antibody), Blood lactate dehydrogenase increased, and Impaired healing.

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

The following safety concerns for Yuflyma are identical to those that have been included in the summary of safety concerns for the reference product Humira® based on the pragmatic assumption that the risks for Yuflyma and the reference product are the same.

Important Identified Risk: Serious infections

TNF-α antagonists, such as adalimumab affect the immune system and their use may affect the body's defence against infection. Fatal and life-threatening infections (including sepsis, opportunistic infections and TB) and Hepatitis B Virus (HBV) reactivation has also been reported with use of adalimumab.

Infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis) are the most commonly reported adverse reactions with the use of adalimumab. There may be a need for dose interruption, for instance before surgery or if a serious infection occurs. Patients must therefore be monitored closely for infections, including TB, before, during and after treatment with Yuflyma, as the elimination of adalimumab may take up to four months.

The use of Yuflyma is contraindicated in patients with active TB or other severe infections such as sepsis, and opportunistic infections.

Risk-benefit impact:

The benefit of Yuflyma as an effective treatment for RA, JIA, axial SpA, PsA, Ps, paediatric plaque Ps, HS, CD, paediatric CD, UC, paediatric UC, UV, and paediatric UV outweighs the risk of serious infections.

Important Identified Risk: Tuberculosis (TB)

Anti-TNF-α therapy increases the risk of infection, especially TB infection. Recent findings have shown that the physiological TNF-mediated signaling was somehow impaired by TNF antagonists, leading to the exacerbation of chronic infection associated with aberrant granuloma formation and maintenance. Although both receptor and antibody agents appear to pose an equally high risk in causing development of new TB infections, monoclonal anti-TNF-α antibody seems more inclined to reactivate latent TB infection (Xie *et al.*, 2014).

TB, including reactivation and new onset of TB, has been reported in patients receiving adalimumab with uncommon frequency. Reports included cases of pulmonary and extra-pulmonary (i.e. disseminated) TB. Yuflyma is contraindicated in patients with TB.

Risk-benefit impact:

The benefit of Yuflyma as an effective treatment for RA, JIA, axial SpA, PsA, Ps, paediatric plaque Ps, HS, CD, paediatric CD, UC, paediatric UC, UV, and paediatric UV outweighs the risk of TB.

Important Identified Risk: Malignancies

In the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies including lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients, though, the occurrence was rare. In the post-marketing setting, cases of leukaemia have been reported in patients treated with a TNF-antagonist. There is an increased background risk for lymphoma and leukaemia in RA patients with long-standing, highly active, inflammatory disease, which complicates the risk estimation. With the current knowledge, a possible risk for the development of lymphomas, leukaemia, and other malignancies in patients treated with a TNF-antagonist cannot be excluded. Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy ≤ 18 years of age), including adalimumab in the post marketing setting. Approximately, half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. No studies have been conducted that include patients with a history of malignancy or in whom treatment with reference product Humira® is continued following development of malignancy. However, a risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

Risk-benefit impact:

The benefit of Yuflyma as an effective treatment for RA, JIA, axial SpA, PsA, Ps, paediatric plaque Ps, HS, CD, paediatric CD, UC, paediatric UC, UV, and paediatric UV outweighs the risk of malignancies.

Important Identified Risk: Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis [ON])

Adalimumab has been seen to be associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of Central Nervous System (CNS) demyelinating disease including MS and ON, and peripheral demyelinating disease, including GBS. Also, there is a known association between intermediate UV and central demyelinating disorders. Therefore,

neurologic evaluation should be performed in patients with non-infectious intermediate UV prior to the initiation of Yuflyma therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.

Risk-benefit impact:

The benefit of Yuflyma as an effective treatment for RA, JIA, axial SpA, PsA, Ps, paediatric plaque Ps, HS, CD, paediatric CD, UC, paediatric UC, UV, and paediatric UV outweighs the risk of demyelinating disorders (including MS, GBS and ON).

Important Identified Risk: BCG disease following live BCG vaccination in infants with *in utero* exposure to Yuflyma

Adalimumab crosses the placenta and has been detected up to five months in the serum of infants born to women treated with adalimumab during pregnancy. BCG vaccine, which contains a live, attenuated strain of M. bovis, may leads to vaccine related AEs to the immunocompromised infants due to *in utero* exposure of Yuflyma. Therefore, administration of live vaccines (e.g., BCG vaccine) to infants exposed to adalimumab *in utero* is not recommended for five months following the mother's last adalimumab injection during pregnancy.

No studies have been conducted that include patients receiving live or live-attenuated vaccine. Furthermore, women with pregnancy or planning to become pregnant were also excluded from clinical development programme.

Risk-benefit impact:

The benefit of Yuflyma as an effective treatment for RA, JIA, axial SpA, PsA, Ps, paediatric plaque Ps, HS, CD, paediatric CD, UC, paediatric UC, UV, and paediatric UV outweighs the risk of BCG disease following live BCG vaccination in infants with *in utero* exposure to Yuflyma.

Important Potential Risk: Progressive multifocal leukoencephalopathy (PML)

PML is a rare, typically fatal, demyelinating disease of the brain caused by activation of the John Cunningham (JC) virus. It is a reported complication of a variety of autoimmune rheumatic diseases and is associated with both synthetic and biologic immunosuppressive agents. PML has been reported with TNF inhibitors in the setting of autoimmune diseases. The epidemiology of PML in such settings is difficult to clearly define, as it is rarely reported and also remains underdiagnosed because of the uncertain nature of the risk associated with the underlying indication for immunosuppressive therapy (Molloy and Calabrese, 2012). Immunocompromised patients were excluded from clinical studies of Yuflyma.

Risk-benefit impact:

The benefit of Yuflyma as an effective treatment for RA, JIA, axial SpA, PsA, Ps, paediatric plaque Ps, HS, CD, paediatric CD, UC, paediatric UC, UV, and paediatric UV outweighs the risk of PML.

Important Potential Risk: Reversible posterior leukoencephalopathy syndrome (RPLS)

RPLS is a generally treatable disorder that is diagnosed based on clinical symptoms (e.g., altered mental status, visual abnormalities, headache, and seizures) and neuroradiographic changes (e.g., cerebral oedema). It is classically associated with malignant hypertension and

immunosuppressive medications. Symptoms usually resolve over time, or with treatment of the underlying cause (Ladizinski *et al.,* 2013).

Risk-benefit impact:

The benefit of Yuflyma as an effective treatment for RA, JIA, axial SpA, PsA, Ps, paediatric plaque Ps, HS, CD, paediatric CD, UC, paediatric UC, UV, and paediatric UV outweighs the risk of RPLS.

Important Potential Risk: Adenocarcinoma of colon in ulcerative colitis (UC) patients

TNF-α plays an important role in the immune response. Its suppression with a TNF-α inhibitor (e.g. adalimumab) might contribute to a reduced immune response, which may further increase the risk of developing colon dysplasia and malignancies such as adenocarcinoma of colon.

With current data it is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer. All patients with UC who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing UC or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations.

Risk-benefit impact:

The benefit of Yuflyma as an effective treatment for RA, JIA, axial SpA, PsA, Ps, paediatric plaque Ps, HS, CD, paediatric CD, UC, paediatric UC, UV, and paediatric UV outweighs the risk of adenocarcinoma of colon in UC patients.

Missing Information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with Crohn's disease (CD)

Risk-benefit impact:

Clinical data up to 5 years exposure to adalimumab is available, however, long-term safety of adalimumab beyond 5 years in the treatment of children aged from 6 years to less than 18 years with CD is not available. Furthermore, Patients aged from 6 years to less than 18 years with CD were not included in clinical studies of Yuflyma. Therefore, children with CD need to be further characterised using the post-marketing data of Yuflyma.

The impact on risk-benefit on the indicated population is unknown.

Missing Information: Episodic treatment in psoriasis (Ps), ulcerative colitis (UC), and juvenile idiopathic arthritis (JIA)

Risk-benefit impact:

This safety concern has been included based on the reference product Humira®. In the clinical development programme, no studies were conducted to specifically evaluate the effect of episodic treatment in Ps, UC, and JIA patients.

The impact on risk-benefit on the indicated population is unknown.

Missing Information: Long-term safety information in the treatment of children with uveitis

Risk-benefit impact:

Adalimumab is a recombinant human IgG1 monoclonal antibody specific for human TNF-α. Adalimumab has shown efficacy in treating refractory UV in multiple settings, including idiopathic disease, JIA, sarcoidosis, Behçet's disease, and UV secondary to spondyloarthropathies, among several other noninfectious UV conditions. However, there is a limited long-term safety information (Balevic and Rabinovich, 2016).

The impact on risk-benefit on the indicated population is unknown.

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

To be harmonised with the list of safety concerns of the reference product, Humira according to the most up-to-date Humira RMP version 16.2, the missing information "Long-term safety information in the treatment of children with uveitis" has been removed and missing information "Episodic treatment in Ps, UC and JIA" has been reclassified to "Episodic treatment in UC" in the list of safety concerns of Yuflyma.

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

The data available for the assessment of the risk of Yuflyma (CT-P17) are effectively derived from two clinical trials in patients with moderate to severe RA (Study CT-P17 3.1 and CT-P17 3.2).

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

Important Identified Risk: Serious infections

Potential mechanisms:

Immunosuppression.

Evidence source(s) and strength of evidence:

In patients treated with adalimumab, respiratory tract infections have been reported to occur very commonly, whereas, intestinal infections, skin and soft tissue infections, reproductive and urinary tract infections etc. have been commonly reported. Meningitis and brain infections, TB and eye infections are uncommon (Humira® Summary of Product Characteristics [SmPC]).

Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC) and clinical trials of Yuflyma.

Characterisation of the risk:

Frequency:

Indication – Rheumatoid Arthritis				
Studies included: CT-P17 3.1 and CT-P17 3.2				
Treatment	**CT-P17**			**Adalimumab Reference Product**
	CT-P17 Total	**CT-P17 Only**	**Switched from reference product***	
N	538	386	152	324
Total No. of TEAEs	8	7	1	7
No. of Subjects with TEAEs [1] n (%)	8 (1.5%)	7 (1.8%)	1 (0.7%)	7 (2.2%)
95% CI for proportion of patients with TEAEs	(0.64, 2.91)	(0.73, 3.70)	(0.02, 3.61)	(0.87, 4.40)

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

MedDRA dictionary, version 22.0

* Subjects in Study CT-P17 3.1, switched to CT-P17 from reference product after completion of Week 24 Treatment.

Seriousness/outcomes:

Indication – Rheumatoid Arthritis				
Studies included: CT-P17 3.1 and CT-P17 3.2				
Treatment	**CT-P17**			**Adalimumab Reference Product**
	CT-P17 Total	**CT-P17 Only**	**Switched from reference product***	
N	538	386	152	324
No. of Subjects with TEAEs [1] n (%)	8 (1.5%)	7 (1.8%)	1 (0.7%)	7 (2.2%)
Serious [2]	8 (1.5%)	7 (1.8%)	1 (0.7%)	7 (2.2%)
Outcomes [3]				
Missing	0	0	0	0
Recovered	7 (1.3%)	7 (1.8%)	0	6 (1.9%)
Recovering	1 (0.2%)	0	1 (0.7%)	0
Did not recover	0	0	0	1 (0.3%)
Fatal	0	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences

[2] Only the most serious event is counted - Seriousness: Serious > Non-serious

[3] Only the most severe outcome is counted - Outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown + Missing

* Subjects in Study CT-P17 3.1, switched to CT-P17 from reference product after completion of Week 24 Treatment.

Severity and nature of risk:

Indication – Rheumatoid Arthritis				
Studies included: CT-P17 3.1 and CT-P17 3.2				
Treatment	**CT-P17**			**Adalimumab Reference Product**
	CT-P17 Total	**CT-P17 Only**	**Switched from reference product***	
N	538	386	152	324
No. of Subjects with TEAEs [1] n (%)	8 (1.5%)	7 (1.8%)	1 (0.7%)	7 (2.2%)
Severity [2]				
Missing	0	0	0	0
Grade 1	0	0	0	0
Grade 2	0	0	0	0
Grade 3	7 (1.3%)	6 (1.6%)	1 (0.7%)	7 (2.2%)
Grade 4	1 (0.2%)	1 (0.3%)	0	0
Grade 5	0	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences

[2] Only the most severe event is counted - Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing

* Subjects in Study CT-P17 3.1, switched to CT-P17 from reference product after completion of Week 24 Treatment.

Risk factors and risk groups:

Risk factors for infection, in general, include very young people and elderly people, immunosuppressive medications (such as transplant recipients), including steroids; treatment with chemotherapy drugs or radiation; removal of the spleen; long-standing diabetes, acquired immune deficiency syndrome (AIDS), or large burns or severe trauma.

Preventability:

Yuflyma is contraindicated in patients with active TB or other severe infections such as sepsis, and opportunistic infections.

Patients must be monitored closely for infections, including TB, before, during and after treatment with Yuflyma. Elimination of adalimumab may take up to four months, therefore, monitoring should be continued throughout this period.

Treatment with Yuflyma should not be initiated in patients with active infections including chronic or localised infections until infections are controlled. In addition, patients who develop a new infection while undergoing treatment with Yuflyma should be monitored closely and undergo a complete diagnostic evaluation. Administration of Yuflyma should be discontinued, if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled. Physicians should exercise caution when considering the use of Yuflyma in patients with a history of recurring infection or with

underlying conditions which may predispose patients to infections, including the use of concomitant immunosuppressive medications.

Impact on the risk-benefit balance of the product:

Yuflyma is a biosimilar medicinal product to the reference product Humira®. Yuflyma and its reference product Humira® contain the same active substance. In accordance with the EU requirements, Yuflyma has been shown to have a comparable quality, safety and efficacy profile to Humira®. Therefore, as for Humira®, the benefit of an effective treatment with Yuflyma outweighs the identified risk of serious infections.

Public health impact:

Yuflyma is contraindicated for use in patients with active TB or other severe infections such as sepsis, and opportunistic infections. Hence, when the medicinal product is used as recommended, the public health impact of serious infection related events is predicted to be minimal.

Important Identified Risk: Tuberculosis (TB)

Potential mechanisms:

Immunosuppression. Also, TNF-α may play an important role in maintaining the integrity of granulomas.

Evidence source(s) and strength of evidence:

TB, including reactivation and new onset of TB, has been reported in patients receiving adalimumab. There have been pulmonary as well as extra-pulmonary TB (Humira® SmPC).

Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC) and clinical trials of Yuflyma.

Characterisation of the risk:

Frequency:

Indication – Rheumatoid Arthritis				
Studies included: CT-P17 3.1 and CT-P17 3.2				
Treatment	**CT-P17**			**Adalimumab Reference Product**
	CT-P17 Total	**CT-P17 Only**	**Switched from reference product***	
N	538	386	152	324
Total No. of TEAEs	0	0	0	2
No. of Subjects with TEAEs [1] n (%)	0	0	0	2 (0.6%)
95% CI for proportion of patients with TEAEs	(0.00, 0.68)	(0.00, 0.95)	(0.00, 2.40)	(0.07, 2.21)

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

MedDRA dictionary, version 22.0

* Subjects in Study CT-P17 3.1, switched to CT-P17 from reference product after completion of Week 24 Treatment.

Seriousness/outcomes:

Indication – Rheumatoid Arthritis				
Studies included: CT-P17 3.1 and CT-P17 3.2				
Treatment	**CT-P17**			**Adalimumab Reference Product**
	CT-P17 Total	**CT-P17 Only**	**Switched from reference product***	
N	538	386	152	324
No. of Subjects with TEAEs [1] n (%)	0	0	0	2 (0.6%)
Serious [2]	0	0	0	2 (0.6%)
Outcomes [3]				
Missing	0	0	0	0
Recovered	0	0	0	1 (0.3%)
Recovering	0	0	0	0
Did not recover	0	0	0	1 (0.3%)
Fatal	0	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences

[2] Only the most serious event is counted - Seriousness: Serious > Non-serious

[3] Only the most severe outcome is counted - Outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown + Missing

* Subjects in Study CT-P17 3.1, switched to CT-P17 from reference product after completion of Week 24 Treatment.

Severity and nature of risk:

Indication – Rheumatoid Arthritis				
Studies included: CT-P17 3.1 and CT-P17 3.2				
Treatment	**CT-P17**			**Adalimumab Reference Product**
	CT-P17 Total	**CT-P17 Only**	**Switched from reference product***	
N	538	386	152	324
No. of Subjects with TEAEs [1] n (%)	0	0	0	2 (0.6%)
Severity [2]				
Missing	0	0	0	0
Grade 1	0	0	0	0
Grade 2	0	0	0	0
Grade 3	0	0	0	2 (0.6%)
Grade 4	0	0	0	0
Grade 5	0	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences

[2] Only the most severe event is counted - Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing

* Subjects in Study CT-P17 3.1, switched to CT-P17 from reference product after completion of Week 24 Treatment.

Risk factors and risk groups:

Risk factors for TB, in general, include very young people and elderly people, immunosuppressive medications (such as transplant recipients), including steroids; treatment with chemotherapy drugs or radiation; removal of the spleen; long-standing diabetes, AIDS, malnutrition, alcoholism, or large burns or severe trauma.

Preventability:

All patients must be evaluated for both active and inactive ("latent") TB infection before starting treatment with Yuflyma. This evaluation should include a detailed medical assessment of patient history of TB or possible previous exposure to people with active TB and previous and/or current immunosuppressive therapy. Appropriate screening tests (i.e. tuberculin skin test and chest X-ray) should be performed in all patients (local recommendations may apply).

Yuflyma is contraindicated in patients with TB. If active TB is diagnosed, Yuflyma therapy must not be initiated. If latent TB is diagnosed, appropriate treatment must be started with anti-TB prophylaxis treatment before the initiation of Yuflyma and in accordance with local recommendations.

In addition, use of anti-TB prophylaxis treatment should also be considered before the initiation of Yuflyma in patients with several or significant risk factors for TB despite a negative test for

TB and in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients should be instructed to seek medical advice if signs/symptoms suggestive of a TB infection (e.g., persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with Yuflyma.

Impact on the risk-benefit balance of the product:

Yuflyma is a biosimilar medicinal product to the reference product Humira®. Yuflyma and its reference product Humira® contain the same active substance. In accordance with the EU requirements, Yuflyma has been shown to have a comparable quality, safety and efficacy profile to Humira®. Therefore, as for Humira®, the benefit of an effective treatment with Yuflyma outweighs the identified risk of TB.

Public health impact:

The potential public health impact is not known.

Important Identified Risk: Malignancies

Potential mechanisms:

The mechanism is not understood. However, immunosuppression may play a role in allowing the proliferation of tumour cells.

TNF has been shown to exert cytotoxic and/or cytostatic effects on a number of human and murine tumour cell lines. Low doses of TNF can increase tumour blood vessel permeability, thus augmenting tissue concentrations of chemotherapeutic agents, as well as enhance the cytolytic effect of Natural killer (NK) and CD8+ T-cell killing of immunogenic tumour cells. Therefore the neutralisation of TNF by adalimumab may allow some types of tumour cells to survive.

Evidence source(s) and strength of evidence:

Malignancies (some fatal) have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-blocking agents including adalimumab in the post marketing setting. Approximately half the cases were lymphomas and rarely, hepatosplenic T-cell lymphoma have been also reported in patients treated with adalimumab (Humira® SmPC).

Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC) and clinical trials of Yuflyma.

Characterisation of the risk:

Frequency:

Indication – Rheumatoid Arthritis				
Studies included: CT-P17 3.1 and CT-P17 3.2				
	CT-P17			**Adalimumab Reference Product**
Treatment	**CT-P17 Total**	**CT-P17 Only**	**Switched from reference product***	
N	538	386	152	324
Total No. of TEAEs	1	1	0	1
No. of Subjects with TEAEs [1] n (%)	1 (0.2%)	1 (0.3%)	0	1 (0.3%)
95% CI for proportion of patients with TEAEs	(0.00, 1.03)	(0.01, 1.43)	(0.00, 2.40)	(0.01, 1.71)

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

MedDRA dictionary, version 22.0

* Subjects in Study CT-P17 3.1, switched to CT-P17 from reference product after completion of Week 24 Treatment.

Seriousness/outcomes:

Indication – Rheumatoid Arthritis				
Studies included: CT-P17 3.1 and CT-P17 3.2				
	CT-P17			**Adalimumab Reference Product**
Treatment	**CT-P17 Total**	**CT-P17 Only**	**Switched from reference product***	
N	538	386	152	324
No. of Subjects with TEAEs [1] n (%)	1 (0.2%)	1 (0.3%)	0	1 (0.3%)
Serious [2]	1 (0.2%)	1 (0.3%)	0	1 (0.3%)
Outcomes [3]				
Missing	0	0	0	0
Recovered	0	0	0	1 (0.3%)
Recovering	0	0	0	0
Did not recover	1 (0.2%)	1 (0.3%)	0	0
Fatal	0	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences

[2] Only the most serious event is counted - Seriousness: Serious > Non-serious

[3] Only the most severe outcome is counted - Outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown + Missing

* Subjects in Study CT-P17 3.1, switched to CT-P17 from reference product after completion of Week 24 Treatment.

Severity and nature of risk:

Indication – Rheumatoid Arthritis				
Studies included: CT-P17 3.1 and CT-P17 3.2				
	CT-P17			**Adalimumab Reference Product**
Treatment	**CT-P17 Total**	**CT-P17 Only**	**Switched from reference product***	
N	538	386	152	324
No. of Subjects with TEAEs [1] n (%)	1 (0.2%)	1 (0.3%)	0	1 (0.3%)
Severity [2]				
Missing	0	0	0	0
Grade 1	0	0	0	0
Grade 2	0	0	0	1 (0.3%)
Grade 3	1 (0.2%)	1 (0.3%)	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences

[2] Only the most severe event is counted - Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing

* Subjects in Study CT-P17 3.1, switched to CT-P17 from reference product after completion of Week 24 Treatment.

Risk factors and risk groups:

History of malignancy, immunosuppressant therapy (e.g., chemotherapy or steroids), and/or AIDS or human immunodeficiency virus (HIV) infection may increase the risk of malignancy. Exposure to sunlight is the main risk factor for most skin cancers. Phototherapy for Ps also increases the risk of skin cancer. UC is associated with a higher risk of colon cancer.

Preventability:

Caution should be exercised when considering TNF-α antagonist therapy for patients with a history of malignant disease or when considering continuing treatment in patients who develop any form of malignancy. Caution should also be exercised in considering treatment of patients with increased risk of malignancy due to heavy smoking. In addition, all patients, and in particular patients with a medical history of extensive immunosuppressant therapy or Ps patients with a history of psoralen and ultraviolet A (PUVA) photochemotherapy treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with adalimumab.

With current data it is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer. Therefore, all patients with UC who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing UC or primary sclerosing

cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations.

Impact on the risk-benefit balance of the product:

Yuflyma is a biosimilar medicinal product to the reference product Humira®. Yuflyma and its reference product Humira® contain the same active substance. Yuflyma has been shown to have a comparable quality, safety and efficacy profile to Humira®. Therefore, as for Humira®, the benefit of an effective treatment with Yuflyma outweighs the identified risk of malignancies.

Public health impact:

Not assessable. The impact on the patient will depend on the nature of the malignancy.

Important Identified Risk: Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis [ON])

Potential mechanisms:

The exact mechanism is not known.

However, in an attempt to clarify the potential biological role of TNF-α blockers in triggering or aggravating demyelination, several theories have been proposed in the literature (Kemanetzoglou *et al.,* 2017, Sedger and McDermott, 2014):

- TNF-α blockers cannot penetrate the intact blood–brain barrier to suppress demyelination but they can enhance demyelination through increased ingress of peripheral autoreactive T-cells into the CNS (lack of entry theory). This theory provides a possible explanation for the failure of anti-TNF-α blockers in reducing demyelination and for their effect on aggravating MS (Robinson *et al.,* 2001, Kaltsonoudis *et al.,* 2014).
- TNF-α blockers may aggravate CNS demyelination by decreasing TNFR2 receptors, which are necessary for the proliferation of immature oligodendrocytes and myelin repair (Cisternas *et al.,* 2002, Titelbaum *et al.,* 2005, Ruiz-Jimeno *et al.,* 2006, Dubcenco *et al.,* 2006, Toussirot *et al.,* 2006, Noseworthy *et al.,* 2000, Van Boxel-Dezaire *et al.,* 1999).
- TNF-α blockers could alter cytokine responses by downregulating interleukin-10 and upregulating interleukin-12 and interferon-γ, creating a profile similar to that of MS patients (Van Boxel-Dezaire *et al., 1*999, Miller *et al.,* 2015, Bellesi *et al.,* 2006).
- TNF-α blockers may deactivate TNF-α systemically, but not within the CNS (due to blood-brain barrier (BBB) impermeability), leading to a high concentration of TNF-α in the CNS ("sponge effect") (Robinson *et al.*, 2001, Kaltsonoudis *et al.,* 2014).
- There may be systematic dysregulation of TNF-α in patients with relapsing remitting MS, as was shown in a recent study of Mausner-Fainberg *et al.* 2015 in which increased serum neutralization capacity of TNF-α in Relapsing-remitting phase of MS (RRMS) patients was observed. These findings offer a possible explanation for the demyelinating events after TNF-α blockade.

- Finally, TNF-α blockers may unmask an underlying latent infection, which can lead to autoimmune demyelination (Kaltsonoudis *et al.*, 2014, Caminero *et al.*, 2011, Bernatsky *et al.,* 2010, Voulgari *et al.,* 2005).

Evidence source(s) and strength of evidence:

TNF-antagonists including adalimumab have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of CNS demyelinating disease including MS and ON, and peripheral demyelinating disease, including GBS.

The role that TNF plays as an immunomodulator suggests that TNF blockade may promote the development of drug-induced neuropathies by augmenting the number of activated peripheral T-cells and thereby enhance autoimmune responses by altering antigen presenting cell function, potentiating T–cell receptor signalling, and/or decreasing apoptosis of autoreactive T-cells. These autoreactive T-cells might also drive the maturation of B cells into cells secreting autoantibodies to neuronal-specific antigens. A recent report in a murine model of experimental autoimmune encephalomyelitis suggests that membrane TNF is neuroprotective. Since TNF inhibitors can neutralise both soluble and membrane TNF, they may remove the neuroprotection provided by membrane TNF. Furthermore, an increasing number of neurologic side effects with the use of TNF-α Blockers have been reported in the literature, consisting of central and peripheral nervous system demyelinating events (Kemanetzoglou E *et al.,* 2017).

Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC).

Characterisation of the risk:

Frequency:

There are no data. Demyelinating disorders have not been observed in clinical studies with CT-P17.

Seriousness/outcomes:

There are no data. Demyelinating disorders have not been observed in clinical studies with CT-P17.

Severity and nature of risk:

There are no data. Demyelinating disorders have not been observed in clinical studies with CT-P17.

Risk factors and risk groups:

Patients with a history of demyelinating disorders, or a family history may be at greater risk.

Preventability:

Preventability of the development of demyelination is not known. In patients with pre-existing or recent onset central or peripheral nervous system demyelinating disorders, the benefits and risks of Yuflyma treatment should be carefully considered before initiation of Yuflyma therapy and discontinuation of Yuflyma therapy should be considered if signs or symptoms of demyelinating disorders develop.

There is a known association between intermediate UV and central demyelinating disorders. Therefore, it has been advised that neurologic evaluation should be performed in patients with non-infectious intermediate UV prior to the initiation of Yuflyma therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.

Impact on the risk-benefit balance of the product:

Yuflyma is a biosimilar medicinal product to the reference product Humira®. Yuflyma and its reference product Humira® contain the same active substance. Yuflyma has been shown to have a comparable quality, safety and efficacy profile to Humira®. Therefore, as for Humira®, the benefit of an effective treatment with Yuflyma outweighs the identified risk of demyelinating disorders (including MS, GBS and ON).

Public health impact:

Demyelinating disorders (e.g. MS, GBS and ON) during the treatment with adalimumab are rare. The public health impact is likely to be minimal.

Important Identified Risk: BCG disease following live BCG vaccination in infants with *in utero* exposure to Yuflyma

Potential mechanisms:

TNF acts to regulate and enhance appropriate inflammatory, innate and adaptive immune responses to pathogenic organisms (Hehlgans and Pfeffer, 2005), and hence inhibition of TNF by adalimumab may suppress these beneficial activities of TNF and increase the potential for

infection. Adalimumab crosses the placenta into infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection.

Evidence source(s) and strength of evidence:

Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC).

Characterisation of the risk:

Frequency:

There are no data. Exposure *in utero* has not been reported in clinical studies with CT-P17.

Seriousness/outcomes:

There are no data. Exposure *in utero* has not been reported in clinical studies with CT-P17.

Severity and nature of risk:

There are no data. Exposure *in utero* has not been reported in clinical studies with CT-P17.

Risk factors and risk groups:

No epidemiological data available.

Preventability:

Patients on Yuflyma may receive concurrent vaccinations, except for live vaccines. Administration of live vaccines (e.g., BCG vaccine) to infants exposed to adalimumab *in utero* is not recommended for five months following the mother's last adalimumab injection during pregnancy.

Impact on the risk-benefit balance of the product:

Yuflyma is a biosimilar medicinal product to the reference product Humira®. Yuflyma and its reference product Humira® contain the same active substance. In accordance with the EU requirements, Yuflyma has been shown to have a comparable quality, safety and efficacy profile to Humira®. Therefore, as for Humira®, the benefit of an effective treatment with Yuflyma outweighs the identified risk of BCG disease following live BCG vaccination in infants with *in utero* exposure to Yuflyma.

Public health impact:

The potential public health impact is not known.

Important Potential Risk: Progressive multifocal leukoencephalopathy (PML)

Potential mechanisms:

Immunosuppression.

Evidence source(s) and strength of evidence:

PML is a reported complication of a variety of autoimmune rheumatic diseases (ARDs) and is associated with both synthetic and biologic immunosuppressive agents (Molloy and Calabrese, 2012). Although JC virus antibodies are present in about 80% of adults, PML occurs primarily in immunocompromised individuals and is thought to be caused by JC virus reactivation. As a

result, PML has been reported primarily in patients with underlying immunosuppressive conditions (i.e., HIV infection, AIDS, malignancies) and immunosuppressive medications. In addition, results from a study of a national hospital discharge database also suggested that rheumatic diseases, including Systemic Lupus Erythematosus (SLE) and RA, are associated with a higher rate of PML compared to the background population (Kothary *et al.,* 2011).

PML has also been reported with TNF inhibitors in the setting of autoimmune diseases (Molloy and Calabrese, 2012). Since, TNF-α plays a critical role in recruiting and activating macrophages, NK cells, T-cells, and antigen presenting cells, depletion of TNF by treatment with TNF-α blockade may facilitate reactivation of JC virus infection and progression to PML (Sammut *et al.,* 2016).

Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC).

Characterisation of the risk:

Frequency:

There are no data. PML has not been observed in clinical studies with CT-P17.

Seriousness/outcomes:

There are no data. PML has not been observed in clinical studies with CT-P17.

Severity and nature of risk:

There are no data. PML has not been observed in clinical studies with CT-P17.

Risk factors and risk groups:

PML occurs predominantly among severely immunosuppressed patients (e.g., due to chemotherapy, or HIV/AIDS). An analysis of PML cases found approximately 40% of patients were aged 40 to 49 years and 75% were male. Currently, over 80% of PML cases are diagnosed in patients with HIV/AIDS. Prior to the era of HIV and AIDS, more than 60% of PML cases were seen in patients with malignancies of the lymphoid (immune) system. Other immunosuppressive conditions that put patients at risk of developing PML include malignancies, organ transplants, and some rheumatic diseases.

Preventability:

There are no known effective preventive measures.

Impact on the risk-benefit balance of the product:

Yuflyma is a biosimilar medicinal product to the reference product Humira®. Yuflyma and its reference product Humira® contain the same active substance. In accordance with the EU requirements, Yuflyma has been shown to have a comparable quality, safety and efficacy profile to Humira®. Therefore, as for Humira®, the benefit of an effective treatment with Yuflyma outweighs the identified risk of PML to Yuflyma.

Public health impact:

The potential public health impact is not known.

Important Potential Risk: Reversible posterior leukoencephalopathy syndrome (RPLS)

Potential mechanisms:

Immunosuppression. The mechanism of the RPLS is possibly the cytotoxic effects of immunosuppressive agents on the vascular endothelium.

Toxins or drugs are the most common causes of RPLS, and have been reported as the etiology in up to 61% of patients (Mishra and Seril, 2018). RPLS is an increasingly documented neurologic disorder that has been reported with the use of systemic and biologic agents in the treatment of rheumatologic conditions. It is generally a treatable condition with symptoms that include altered mental status, headaches, visual disturbances, and seizures along with distinctive findings on neuroimaging studies (Dickson and Menter, 2017).

Reversible, predominantly posterior leukoencephalopathy may develop in patients who are immunosuppressed. The cause of the RPLS is multifactorial. The syndrome should be promptly recognized, since it is reversible and readily treated by discontinuing the offending immunosuppressive agent or decreasing the dose (Hinchey *et al.,* 1996).

Evidence source(s) and strength of evidence:

Two cases (Mahévas T *et al.,* 2015, Nwafo N, 2018) have reported an association between RPLS and adalimumab. RPLS has also been reported in subjects treated with other medicines similar to adalimumab (Kastrup and Diener*,* 2008, Zamvar *et al.,* 2009, Haddock R *et al.,* 2011, Garg N *et al.,* 2013).

Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC).

Characterisation of the risk:

Frequency:

There are no data. RPLS has not been observed in clinical studies with CT-P17.

Seriousness/outcomes:

There are no data. RPLS has not been observed in clinical studies with CT-P17.

Severity and nature of risk:

There are no data. RPLS has not been observed in clinical studies with CT-P17.

Risk factors and risk groups:

Risk factors include high blood pressure (BP) (including high BP in pregnancy) and use of medicines known as calcineurin inhibitors.

Preventability:

The risk of RPLS may be reduced by maintaining normotensive BPs.

Impact on the risk-benefit balance of the product:

Yuflyma is a biosimilar medicinal product to the reference product Humira®. Yuflyma and its reference product Humira® contain the same active substance. In accordance with the EU requirements, Yuflyma has been shown to have a comparable quality, safety and efficacy profile

to Humira®. Therefore, as for Humira®, the benefit of an effective treatment with Yuflyma outweighs the potential risk of RPLS to Yuflyma.

Public health impact:

The potential public health impact is not known.

Important Potential Risk: Adenocarcinoma of colon in ulcerative colitis (UC) patients

Potential mechanisms:

TNF-α plays an important role in the immune response. Its suppression with a TNF-α inhibitor such as adalimumab might contribute to a reduced immune response, increasing the risk of developing colon dysplasia and malignancies such as adenocarcinoma of colon.

TNF has been shown to exert cytotoxic and/or cytostatic effects on a number of human and murine tumour cell lines. Low doses of TNF can increase tumour blood vessel permeability, thus augmenting tissue concentrations of chemotherapeutic agents, as well as enhance the cytolytic effect of NK and CD8+ T-cell killing of immunogenic tumour cells. Therefore, the neutralisation of TNF by adalimumab may allow some types of tumour cells to survive.

Evidence source(s) and strength of evidence:

In a review of published studies concerning the risk of colon cancer in UC patients, the yearly incidence rate of colon cancer ranged from approximately 0.006% to 0.16%.

Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC).

Characterisation of the risk:

Frequency:

There are no data. CT-P17 has not been studied in UC patients.

Seriousness/outcomes:

There are no data. CT-P17 has not been studied in UC patients.

Severity and nature of risk:

There are no data. CT-P17 has not been studied in UC patients.

Risk factors and risk groups:

Factors associated with an increased risk of colon cancer include age greater than 50 years, presence of colon polyps, personal or family history of some cancers, duration of UC, extent and severity of UC, diet, and cigarette smoking.

Preventability:

All patients with UC who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing UC or primary sclerosing cholangitis), or who have a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course.

Impact on the risk-benefit balance of the product:

Yuflyma is a biosimilar medicinal product to the reference product Humira®. Yuflyma and its reference product Humira® contain the same active substance. In accordance with the EU requirements, Yuflyma has been shown to have a comparable quality, safety and efficacy profile to Humira®. Therefore, as for Humira®, the benefit of an effective treatment with Yuflyma outweighs the potential risk of adenocarcinoma of colon.

Public health impact:

The public health impact is not known.

SVII.3.2. Presentation of the missing information

Missing Information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with Crohn's disease (CD)

Evidence source:

People may be treated with Yuflyma for longer than they have been in clinical studies. Some safety concerns, such as malignancy, may take a long time to develop. Yuflyma acts by interfering with the normal functioning of the immune system. There may be long-term consequences that have not yet been seen in patients that have been studied so far.

Population in need of further characterisation:

Clinical data up to 5 years exposure of adalimumab is available, however, long-term safety of adalimumab in the treatment of children aged from 6 years to less than 18 years with CD needs to be further characterised.

Missing Information: Episodic treatment in ulcerative colitis (UC)

Evidence source:

There was no experience of adalimumab used as episodic treatment for UC in clinical trials. CT-P17 was also not studied as episodic treatment in the indication.

Population in need of further characterisation:

The safety and efficacy of Yuflyma have not been established in the subjects with episodic treatment for UC. However, it is possible that Yuflyma may be prescribed for the episodic treatment of the indication.

Missing Information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis

Evidence source:

Clinical trial for the treatment of paediatric patients with UC was not conducted with CT-P17. In addition, historical data of the studies with adalimumab in the treatment of paediatric patients with UC are inadequate for the assessment of long-term safety. However some safety concerns, such as malignancy, may take a long time to develop. Considering adalimumab acts by

interfering with normal functioning of the immune system, there may be long-term consequences that have not yet been seen in patients who have been studied so far.

Population in need of further characterisation:

The long-term safety of adalimumab in the treatment of paediatric patients with UC has not been established. However, it is possible that Yuflyma is prescribed for the patients aged from 6 years to less than 18 years with UC, therefore the long-term use in this population needs to be further characterised.

Part II: Module SVIII - Summary of the safety concerns

Table 9 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 [ON]) • BCG disease following live BCG vaccination in infants with *in utero* exposure to Yuflyma
Important potential risks	• Progressive multifocal leukoencephalopathy (PML) • Reversible posterior leukoencephalopathy syndrome (RPLS) • Adenocarcinoma of colon in ulcerative colitis (UC) patients
Missing information	• Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD • Episodic treatment in ulcerative colitis (UC) • Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Not applicable, since no such activities are being conducted or planned.

III.2 Additional pharmacovigilance activities

Not applicable, since no additional pharmacovigilance studies/activities are being conducted or planned.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable, since no additional pharmacovigilance studies/activities are being conducted or planned.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

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

V.1. Routine Risk Minimisation Measures

Table 10 Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk - Serious infections	Routine risk communication: • SmPC sections 4.4 and 4.8. • PL sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance is given in SmPC section 4.2 that the dose interruption may be needed for instance before surgery or if a serious infection occurs. • Use of Yuflyma is contraindicated in patients with severe infections such as sepsis and opportunistic infections as per SmPC section 4.3 and PL section 2. • Warning is given in SmPC section 4.4 and PL section 2 that patients taking TNF-antagonists are more susceptible to serious infections. Therefore, patients must be monitored closely for infections, before, during and after treatment with Yuflyma, as the elimination of adalimumab may take up to four months. • Warning is given in SmPC section 4.4 that the treatment with Yuflyma should not be initiated in patients with active infections including chronic or localised infections until infections are controlled. • Guidance is given in SmPC section 4.4 that the patients who develop a new infection while undergoing treatment with Yuflyma should be monitored closely and undergo a complete diagnostic evaluation. Administration of Yuflyma should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled. • Advice for the physician is given in SmPC section 4.4 and PL section 2 that they should exercise caution when considering the use of Yuflyma in patients with a history of recurring infection or with the underlying conditions which may predispose patients to infections, including the use of concomitant immunosuppressive medications.

	• Warning regarding the occurence of serious infections, including sepsis, due to bacterial, mycobacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis in patients receiving Yuflyma is given in SmPC section 4.4. • Warning is given in SmPC section 4.4 and PL section 2 that the reactivation of hepatitis B can occur in patients receiving a TNF-antagonist including Yuflyma, who are chronic carriers of this virus (i.e. surface antigen positive). Therefore, patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. • Recommendation is given in SmPC sections 4.4, 4.5 and PL section 2 that Yuflyma should not be used concomitantly with other biologic DMARDS (eg, anakinra and abatacept) or other TNF-antagonists because of the possible increased risk of infections including serious infections. • Recommendation is given in SmPC section 4.4 that the patients undergoing surgery while on the treatment with Yuflyma should be closely monitored for infections and appropriate actions should be taken. • Warning is given in SmPC section 4.4 and PL section 2 regarding the higher risk of serious infections among the patients over 65 years of age being treated with Yuflyma. Particular attention regarding the risk for infections should be paid when treating the elderly. • Warning is given in PL sections 2 and 4 to inform the doctor or pharmacist before taking Yuflyma, if the patient, has an infection, including long-term infection or an infection in one part of the body, has symptoms of infection, for example, fever, wounds, feeling tired and dental problems, live or travel in regions where fungal infections (for example, histoplasmosis, coccidioidomycosis or blastomycosis) are very common, have had infections which keep coming back or other conditions that increase the risk of infections. • Warning is given in PL setion 2 that certain live vaccines may cause infections and should not be given while receiving Yuflyma. <u>Other routine risk minimisation measures beyond the Product Information:</u> *Legal status*: Prescription only medicine

Important identified risk - Tuberculosis (TB)	Routine risk communication: SmPC 4.4 and 4.8. PL sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance is given in SmPC section 4.2 that the dose interruption may be needed for instance before surgery or if a serious infection occurs. • Use of Yuflyma is contraindicated in patients with active TB as per SmPC sections 4.3, 4.4 and PL section 2. • Warning is given in SmPC section 4.4 and PL section 2 that patients taking TNF-antagonists are more susceptible to serious infections. Therefore, patients must be monitored closely for infections, including TB before, during and after treatment with Yuflyma, as the elimination of Yuflyma may take up to four months, monitoring should be continued throughout this period. • Warning is given in SmPC section 4.4 that the risk and benefits of treatment with Yuflyma should be considered prior to initiating the therapy with Yuflyma in patients who have been exposed to TB and have travelled in areas of high risk of TB. • Recommendation is given in SmPC section 4.4 and PL section 2 that before starting the treatment with Yuflyma all patients must be evaluated for both active or inactive (“latent”) TB infection. This evaluation should include a detailed medical assessment of patient history of TB, appropriate screening tests, or possible previous exposure to people with active TB and previous and/or current immunosuppressive therapy. Appropriate screening tests (i.e. tuberculin skin test and chest X-ray) should be performed in all patients. It is recommended that the conduct and results of the screening tests to be recorded in the Patient Reminder Card. • Guidance is given for the prescribers in SmPC section 4.4 about the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised. • Advice is given in SmPC section 4.4 that Yuflyma therapy must not be initiated, if active TB is diagnosed. • Advice is given in SmPC section 4.4 that the use of anti-TB prophylaxis treatment should also be considered before the initiation of Yuflyma in patients with several or significant risk factors for TB despite a negative test for TB and in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed.

	• Guidance is given in SmPC section 4.4 that the patients should be instructed to seek medical advice if signs/symptoms suggestive of a TB infection (e.g., persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with Yuflyma. • Guidance is given in PL section 2 that it is very important to inform the doctor in case the patient ever had TB, or if the patient have been in close contact with someone who has had TB. <u>Other routine risk minimisation measures beyond the Product Information:</u> *Legal status*: Prescription only medicine
Important identified risk - Malignancies	<u>Routine risk communication:</u> • SmPC sections 4.4 and 4.8. • PL sections 2 and 4. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> • Guidance is given in SmPC section 4.4 and PL section 2 that hepatosplenic T-cell lymphomas have occurred in young adult patients while Yuflyma and AZA or 6-MP used concomitantly, therefore the combination should be carefully considered. • Warning in SmPC section 4.4 and PL section 2 regarding the occurrence of malignancies including lymphoma, hepatosplenic T-cell lymphoma, leukaemia, or other cancers may increase while undergoing treatment with Yuflyma. • Caution should be exercised while initiating treatment with TNF-antagonist in patients with a history of malignancy, chronic obstructive pulmonary disease and in patients with increased risk for malignancy due to heavy smoking as per SmPC section 4.4 and PL section 2. • Warning is given in SmPC section 4.4 that all the patients, and in particular patients with a medical history of extensive immunosuppressant therapy or Ps patients with a history of PUVA treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with Yuflyma. <u>Other routine risk minimisation measures beyond the Product Information:</u> *Legal status*: Prescription only medicine

Important identified risk - Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis [ON])	Routine risk communication: • SmPC sections 4.4 and 4.8. • PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning is given in SmPC section 4.4 that TNF-antagonists including Yuflyma have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of CNS demyelinating disease including MS and ON, and peripheral demyelinating disease, including GBS. Therefore, the prescriber should exercise caution in considering the use of Yuflyma in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of Yuflyma should be considered if any of these disorders develop. • Warning is given in SmPC section 4.4 that neurologic evaluation should be performed in patients with non-infectious intermediate UV prior to the initiation of Yuflyma therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders. • Warning is given in PL section 2 that if the patient has or develop a demyelinating disease (a disease that affects the insulating layer around the nerves, such as MS), then the doctor will decide if the patient should receive or continue to receive Yuflyma. It is also advised to inform the doctor in case the patient experience symptoms like change in vision, weakness in arms or legs or numbness or tingling in any part of the body. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine
Important identified risk - BCG disease following live BCG vaccination in infants with *in utero* exposure to Yuflyma	Routine risk communication: • SmPC section 4.6. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance is given in SmPC sections 4.4, 4.6 and PL section 2 that Yuflyma may cross the placenta into the serum of infants born to women treated with Yuflyma during pregnancy. Consequently, these infants may be at increased risk for infection. Therefore, administration of live vaccines (e.g., BCG vaccine) to infants exposed to Yuflyma *in utero* is not

	recommended for five months following the mother's last Yuflyma injection during pregnancy. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine
Important potential risk - Progressive multifocal leukoencephalopathy (PML)	Routine risk communication: • None. Routine risk minimisation activities recommending specific clinical measures to address the risk: • None. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine
Important potential risk - Reversible posterior leukoencephalopathy syndrome (RPLS)	Routine risk communication: • None. Routine risk minimisation activities recommending specific clinical measures to address the risk: • None. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine
Important potential risk - Adenocarcinoma of colon in ulcerative colitis (UC) patients	Routine risk communication: • None. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning is given in SmPC section 4.4 that all patients with UC who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing UC or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy with Yuflyma and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. Other routine risk minimisation measures beyond the Product Information: *Legal status:* Prescription only medicine

Missing information - Long-term safety information in the treatment of children aged from 6 years to less than 18 years with Crohn's disease (CD)	Routine risk communication: • None. Routine risk minimisation activities recommending specific clinical measures to address the risk: • None. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine
Missing information - Episodic treatment in ulcerative colitis (UC)	Routine risk communication: • None. Routine risk minimisation activities recommending specific clinical measures to address the risk: • None. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine
Missing information - Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis	Routine risk communication: • None. Routine risk minimisation activities recommending specific clinical measures to address the risk: • None. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine

V.2. Additional Risk Minimisation Measures

Patient Reminder Card

Objectives:

To provide patients with a constant reminder that can be carried in a purse or wallet of the more important safety concerns associated with Yuflyma treatment.

To remind the patient to tell his/her doctor of important symptoms that may suggest that he/she has developed one of the safety concerns on the reminder card.

To provide the patient with a document that he/she can show to any health professional that may not be familiar with the treatment he/she is receiving.

To remind the patient that both he/she and his/her doctor must keep a record of the brand name and batch number of the Yuflyma treatment he/she has received.

To allow the patient to carry a record of screening for TB and the outcome of screening.

Patients must be given a patient reminder card highlighting the following risks:

- Serious infections
- Tuberculosis (TB)
- Malignancies
- Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis [ON])
- BCG disease following live BCG vaccination in infants with *in utero* exposure to Yuflyma

Rationale for the additional risk minimisation activity:

The intent of this patient reminder card is to educate patients on important safety information that they need to be aware of before and during treatment with Yuflyma. Also, to ensure that special information regarding the patient's current therapy and its important risks is held by the patient at all times and reaches the relevant healthcare professional when needed.

Target audience and planned distribution path:

Patients who receive Yuflyma must be given a special reminder card that summarises the safety information about the medicine. The patient reminder card is distributed to healthcare professionals who will subsequently prescribe Yuflyma and provide the Patient Reminder Card to patients treated with Yuflyma.

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

Signal detection: The applied trend analysis tool will compare relative reported frequencies (actual versus historic) as per ADR type according to internal procedure. Obtained ratios, equal or above a value of 3 will be considered a signal and subjected to further signal verification activities. This method will allow the identification of relative changes in reporting frequency, e.g., caused by a decrease in the effectiveness of risk minimisation measures or in the case of

emerging new risk factors and represents a pragmatic quantitative means of monitoring at least secular changes in the frequency of reporting of serious preventable ADRs.

V.3. Summary of risk minimisation measures

Table 11 Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk - Serious infections	Routine risk minimisation measures: • SmPC sections 4.2, 4.3, 4.4, 4.5 and 4.8 • PL section 2 and 4 Legal status: Prescription only medicine Additional risk minimisation measures: Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Important identified risk - Tuberculosis (TB)	Routine risk minimisation measures: • SmPC sections 4.2, 4.3, 4.4 and 4.8. • PL sections 2 and 4 Legal status: Prescription only medicine Additional risk minimisation measures: Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Important identified risk - Malignancies	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8 • PL sections 2 and 4 Legal status: Prescription only medicine Additional risk minimisation measures: Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk - Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis [ON])	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8. • PL sections 2 and 4 Legal status: Prescription only medicine Additional risk minimisation measures: Patient reminder card.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Important identified risk - BCG disease following live BCG vaccination in infants with *in utero* exposure to Yuflyma	Routine risk minimisation measures: • SmPC section 4.4 and 4.6 • PL section 2 Legal status: Prescription only medicine Additional risk minimisation measures: Patient reminder card.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Important potential risk - Progressive multifocal leukoencephalopathy (PML)	Routine risk minimisation measures: Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Important potential risk - Reversible posterior leukoencephalopathy syndrome (RPLS)	Routine risk minimisation measures: Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		Additional pharmacovigilance activities: None
Important potential risk - Adenocarcinoma of colon in ulcerative colitis (UC) patients	Routine risk minimisation measures: • SmPC section 4.4 Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Missing information - Long-term safety information in the treatment of children aged from 6 years to less than 18 years with Crohn's disease (CD)	Routine risk minimisation measures: Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Missing information - Episodic treatment in ulcerative colitis (UC)	Routine risk minimisation measures: Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information - Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis	Routine risk minimisation measures: Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Part VI: Summary of the risk management plan

Summary of risk management plan for Yuflyma® (Adalimumab)

This is a summary of the Risk Management Plan (RMP) for Yuflyma. The RMP details important risks of Yuflyma, how these risks can be minimised, and how more information will be obtained about Yuflyma risks and uncertainties (missing information).

Yuflyma's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how Yuflyma should be used.

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

I. The medicine and what it is used for

Yuflyma is authorised for rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), axial spondyloarthritis (axial SpA) – ankylosing spondylitis (AS) and axial SpA without radiographic evidence of AS, psoriatic arthritis (PsA), psoriasis (Ps), paediatric plaque Ps, hidradenitis suppurativa (HS) (including adolescents from 12 years of age), Crohn's disease (CD), paediatric CD, ulcerative colitis (UC), paediatric UC, uveitis (UV), and paediatric UV (see SmPC for the full indication). It contains adalimumab as the active substance and it is given by subcutaneous route.

Further information about the evaluation of Yuflyma's benefits can be found in Yuflyma's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/yuflyma

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

Important risks of Yuflyma, together with measures to minimise such risks and the proposed studies for learning more about Yuflyma'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 PL 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 Yuflyma, 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 Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

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

II.A List of important risks and missing information

Important risks of Yuflyma 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 Yuflyma. 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 [ON]) • BCG disease following live BCG vaccination in infants with *in utero* exposure to Yuflyma
Important potential risks	• Progressive multifocal leukoencephalopathy (PML) • Reversible posterior leukoencephalopathy syndrome (RPLS) • Adenocarcinoma of colon in ulcerative colitis (UC) patients
Missing information	• Long-term safety information in the treatment of children aged from 6 years to less than 18 years with Crohn's disease (CD) • Episodic treatment in ulcerative colitis (UC) • Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis

II.B Summary of important risks

Important identified risk: Serious infections	
Evidence for linking the risk to the medicine	In patients treated with adalimumab, respiratory tract infections have been reported to occur very commonly, whereas, intestinal infections, skin and soft tissue infections, reproductive and urinary tract infections etc. have been commonly reported. Meningitis and brain infections, TB and eye infections are uncommon (Humira® Summary of Product Characteristics [SmPC]). Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC) and clinical trials of Yuflyma.
Risk factors and risk groups	Risk factors for infection, in general, include very young people and elderly people, immunosuppressive medications (such as transplant recipients), including steroids; treatment with chemotherapy drugs or radiation; removal of the spleen; long-standing diabetes, acquired immune deficiency syndrome (AIDS), or large burns or severe trauma.
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.2, 4.3, 4.4, 4.5 and 4.8 • PL section 2 and 4 Legal status: Prescription only medicine Additional risk minimisation measures: Patient reminder card

Important identified risk: Tuberculosis (TB)	
Evidence for linking the risk to the medicine	TB, including reactivation and new onset of TB, has been reported in patients receiving adalimumab. There have been pulmonary as well as extra-pulmonary TB (Humira® SmPC). Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC) and clinical trials of Yuflyma.
Risk factors and risk groups	Risk factors for TB, in general, include very young people and elderly people, immunosuppressive medications (such as transplant recipients), including steroids; treatment with chemotherapy drugs or radiation; removal of the spleen; long-standing diabetes, AIDS, malnutrition, alcoholism, or large burns or severe trauma.
Risk minimisation measures	Routine risk minimisation measures:

	• SmPC sections 4.2, 4.3, 4.4 and 4.8. • PL sections 2 and 4 Legal status: Prescription only medicine Additional risk minimisation measures: Patient reminder card

Important identified risk: Malignancies	
Evidence for linking the risk to the medicine	Malignancies (some fatal) have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-blocking agents including adalimumab in the post marketing setting. Approximately half the cases were lymphomas and rarely, hepatosplenic T-cell lymphoma have been also reported in patients treated with adalimumab (Humira® SmPC). Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC) and clinical trials of Yuflyma.
Risk factors and risk groups	History of malignancy, immunosuppressant therapy (e.g., chemotherapy or steroids), and/or AIDS or human immunodeficiency virus (HIV) infection may increase the risk of malignancy. Exposure to sunlight is the main risk factor for most skin cancers. Phototherapy for Ps also increases the risk of skin cancer. UC is associated with a higher risk of colon cancer.
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8 • PL sections 2 and 4 Legal status: Prescription only medicine Additional risk minimisation measures: Patient reminder card

Important identified risk: Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis [ON])	
Evidence for linking the risk to the medicine	TNF-antagonists including adalimumab have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system (CNS) demyelinating disease including MS and ON, and peripheral demyelinating disease, including GBS. The role that TNF plays as an immunomodulator suggests that TNF blockade may promote the development of drug-induced

	neuropathies by augmenting the number of activated peripheral T-cells and thereby enhance autoimmune responses by altering antigen presenting cell function, potentiating T–cell receptor signalling, and/or decreasing apoptosis of autoreactive T-cells. These autoreactive T-cells might also drive the maturation of B cells into cells secreting autoantibodies to neuronal-specific antigens. A recent report in a murine model of experimental autoimmune encephalomyelitis suggests that membrane TNF is neuroprotective. Since TNF inhibitors can neutralise both soluble and membrane TNF, they may remove the neuroprotection provided by membrane TNF. Furthermore, an increasing number of neurologic side effects with the use of TNF-α Blockers have been reported in the literature, consisting of central and peripheral nervous system demyelinating events (Kemanetzoglou E *et al.,* 2017). Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC).
Risk factors and risk groups	Patients with a history of demyelinating disorders, or a family history may be at greater risk.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> • SmPC sections 4.4 and 4.8. • PL sections 2 and 4 Legal status: Prescription only medicine <u>Additional risk minimisation measures:</u> Patient reminder card.

Important identified risk: BCG disease following live BCG vaccination in infants with *in utero* exposure to Yuflyma	
Evidence for linking the risk to the medicine	Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC).
Risk factors and risk groups	No epidemiological data available.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> • SmPC section 4.4 and 4.6 • PL section 2 Legal status: Prescription only medicine <u>Additional risk minimisation measures:</u>

	Patient reminder card.

Important potential risk: Progressive multifocal leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	PML is a reported complication of a variety of autoimmune rheumatic diseases (ARDs) and is associated with both synthetic and biologic immunosuppressive agents (Molloy and Calabrese, 2012). Although John Cunningham (JC) virus antibodies are present in about 80% of adults, PML occurs primarily in immunocompromised individuals and is thought to be caused by JC virus reactivation. As a result, PML has been reported primarily in patients with underlying immunosuppressive conditions (i.e., HIV infection, AIDS, malignancies) and immunosuppressive medications. In addition, results from a study of a national hospital discharge database also suggested that rheumatic diseases, including Systemic Lupus Erythematosus (SLE) and RA, are associated with a higher rate of PML compared to the background population (Kothary *et al.,* 2011). PML has also been reported with TNF inhibitors in the setting of autoimmune diseases (Molloy and Calabrese, 2012). Since, TNF-α plays a critical role in recruiting and activating macrophages, NK cells, T-cells, and antigen presenting cells, depletion of TNF by treatment with TNF-α blockade may facilitate reactivation of JC virus infection and progression to PML (Sammut *et al.,* 2016). Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC).
Risk factors and risk groups	PML occurs predominantly among severely immunosuppressed patients (e.g., due to chemotherapy, or HIV/AIDS). An analysis of PML cases found approximately 40% of patients were aged 40 to 49 years and 75% were male. Currently, over 80% of PML cases are diagnosed in patients with HIV/AIDS. Prior to the era of HIV and AIDS, more than 60% of PML cases were seen in patients with malignancies of the lymphoid (immune) system. Other immunosuppressive conditions that put patients at risk of developing PML include malignancies, organ transplants, and some rheumatic diseases.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> Legal status: Prescription only medicine <u>Additional risk minimisation measures:</u> None

Important potential risk: Reversible posterior leukoencephalopathy syndrome (RPLS)	
Evidence for linking the risk to the medicine	Two cases (Mahévas T *et al.,* 2015, Nwafo N, 2018) have reported an association between RPLS and adalimumab. RPLS has also been reported in subjects treated with other medicines similar to adalimumab (Kastrup and Diene,r 2008, Zamvar *et al.,* 2008, Haddock R *et al.,* 2011, Garg N *et al.,* 2013). Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC).
Risk factors and risk groups	Risk factors include high blood pressure (BP) (including high BP in pregnancy) and use of medicines known as calcineurin inhibitors.
Risk minimisation measures	Routine risk minimisation measures: Legal status: Prescription only medicine Additional risk minimisation measures: None

Important potential risk: Adenocarcinoma of colon in ulcerative colitis (UC) patients	
Evidence for linking the risk to the medicine	In a review of published studies concerning the risk of colon cancer in UC patients, the yearly incidence rate of colon cancer ranged from approximately 0.006% to 0.16%. Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC).
Risk factors and risk groups	Factors associated with an increased risk of colon cancer include age greater than 50 years, presence of colon polyps, personal or family history of some cancers, duration of UC, extent and severity of UC, diet, and cigarette smoking.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 Legal status: Prescription only medicine Additional risk minimisation measures: None

Missing information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with Crohn's disease (CD)	
Risk minimisation measures	Routine risk minimisation measures:

	Legal status: Prescription only medicine Additional risk minimisation measures: None

Missing information: Episodic treatment in ulcerative colitis (UC)	
Risk minimisation measures	Routine risk minimisation measures: Legal status: Prescription only medicine Additional risk minimisation measures: None

Missing information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis	
Risk minimisation measures	Routine risk minimisation measures: Legal status: Prescription only medicine Additional risk minimisation measures: None

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Yuflyma.

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

There are no studies required for Yuflyma.

Part VII: Annexes

Table of contents

Annex 4 – Specific adverse drug reaction follow-up forms

Not applicable.

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

Draft key messages of the additional risk minimisation measures

In addition to the Summary of Product Characteristics, an additional risk minimisation measure i.e. "Patient reminder card" will be implemented, mentioned below in detail:

Patient Reminder Card

The patient reminder card contains important safety information that a patient needs to be aware of before and during the treatment with Yuflyma. This reminder card is helpful to the patient as it highlights the risk of serious infections, tuberculosis (TB), malignancies, demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis [ON]) and BCG disease following live BCG vaccination in infants with *in utero* exposure to Yuflyma. The key messages of patient reminder card have been provided below:

Call your/your child's doctor or get medical care right away, if you/your child has any of the following symptoms of these possible serious side effects:

Infections

- Fever, chills, unusual sweating, feeling unwell or more tired than normal, feeling or being sick (such as nausea or vomiting), diarrhoea, stomach pain, loss of appetite or weight loss, cough or coughing up blood or mucus, shortness of breath, problems urinating, skin sores, wounds, muscle aches, dental problems

Cancer

- Night sweats, swelling of the lymph nodes (swollen glands) in the neck, armpits, groin or other areas, weight loss, new skin lesions or change in skin lesions (such as moles or freckles) your child already has, severe itchiness that cannot be explained

Nervous system problems

- Numbness or tingling, vision changes, muscle weakness, unexplained dizziness

For Adult Patients

Before Yuflyma Treatment

Tell your doctor about any health problems you have and any medicines you take. This will help you and your doctor decide if Yuflyma is right for you.

Tell your doctor if you:

- Have an infection or have symptoms of an infection (such as fever, wounds, feeling tired, dental problems);
- Have tuberculosis or have been in close contact with someone with tuberculosis;
- Have or have had cancer;
- Have any numbness or tingling or have a problem that affects your nervous system, such as multiple sclerosis;
- Reside or travel in regions where fungal infections such as histoplasmosis, coccidioidomycosis or blastomycosis are endemic.

Your doctor should check you for signs and symptoms of tuberculosis before starting Yuflyma. You may need to be treated for tuberculosis before you start Yuflyma.

Vaccinations

- You may receive vaccinations except for live vaccines.
- If you receive Yuflyma while you are pregnant, it is important that you inform your baby's doctor before your baby receives any vaccine. Your baby should not receive a 'live vaccine', such as BCG (used to prevent tuberculosis) within 5 months following your last Yuflyma injection during pregnancy.

During Yuflyma Treatment

To make sure that Yuflyma is working properly and safely for you, you should check in with your doctor regularly to discuss how you are doing. Tell your doctor right away about any changes in your condition.

Keep your doctor informed about how Yuflyma is working for you

- It is important to call your doctor right away about any unusual symptoms you may have. This will help make sure you get the right care. It will also lower the chance of a side effect becoming worse.
- Many side effects, including infections, can be managed if you tell your doctor right away.
- If you get a side effect, your doctor will decide if you should continue or stop your Yuflyma treatment. It is important to talk with your doctor to find out what is right for you.
- Since side effects can happen after your last dose of Yuflyma, tell your doctor about any problems that you may have up to 4 months after your last injection of Yuflyma.

Tell your doctor about:

- Any new medical conditions that you have;
- New medicines you are taking;
- Any surgery or operation that you have planned.

Information for you and health care professionals involved in your medical care or treatment:

Your name: _____
Doctor's name
(who prescribed Yuflyma):_____
Doctor's phone number:_____
Indication:_____
Date of your first Yuflyma injection: _____
Dose of your Yuflyma injection: _____
Date of your last Yuflyma injection
(if no longer taking Yuflyma):_____

Tuberculosis (TB) Tests

Please record the date and results of your last screening for TB below:

Tuberculin test: _____

Chest X-ray: _____

For Paediatric Patients

Before Yuflyma Treatment

Tell your child's doctor about any health problems your child has and any medicines your child takes. This will help you and your child's doctor decide if Yuflyma is right for your child.

Tell your child's doctor if your child:

- Has an infection or has symptoms of an infection (such as fever, wounds, feeling tired, dental problems);
- Has tuberculosis or has been in close contact with someone with tuberculosis;
- Has or has had cancer;
- Has any numbness or tingling or has a problem that affects your child's nervous system, such as multiple sclerosis;
- Reside or travel in regions where fungal infections such as histoplasmosis, coccidioidomycosis or blastomycosis are endemic.

Your child's doctor should check him or her for signs and symptoms of tuberculosis before starting Yuflyma. Your child may need to be treated for tuberculosis before he or she starts Yuflyma.

Vaccinations

- Your child's doctor may suggest certain vaccinations for your child before they start Yuflyma. Live vaccines should not be administered to your child while taking Yuflyma. If your child receives Yuflyma while pregnant, it is important that you inform the baby's doctor before the baby receives any vaccine. The baby should not receive a "live vaccine," such as BCG (used to prevent tuberculosis) within 5 months following your child's last Yuflyma injection during pregnancy.

During Yuflyma Treatment

To make sure that Yuflyma is working properly and safely for your child, you should check in with his or her doctor regularly to discuss how your child is doing. Tell your doctor right away about any changes in your child's condition.

Keep your child's doctor informed about how Yuflyma is working for your child.

- It is important to call your child's doctor right away about any unusual symptoms your child may have. This will help make sure your child gets the right care. It will also lower the chance of a side effect becoming worse.
- Many side effects, including infections, can be managed if you tell your child's doctor right away.

- If your child gets a side effect, your child's doctor will decide if your child should continue or stop his or her Yuflyma treatment. It is important to talk with your child's doctor to find out what is right for your child.
- Since side effects can happen after your child's last dose of Yuflyma, tell your child's doctor about any problems that your child may have up to 4 months after your child's last injection of Yuflyma.

Tell your child's doctor about:

- Any new medical conditions that your child has;
- New medicines your child is taking;
- Any surgery or operation that is planned for your child;

Information for you and health care professionals involved in your child's medical care or treatment:

Your child's name: _____
Your child's doctor's name
(who prescribed Yuflyma):_____
Your child's doctor's phone number: _____
Indication: _____
Date of your child's first Yuflyma injection: _____
Dose of your child's Yuflyma injection: _____
Date of your child's last Yuflyma injection
(if no longer taking Yuflyma):_____

Tuberculosis (TB) Tests

Please record the date and results of your child's last screening for TB below:
Tuberculin test: _____
Chest X-ray: _____