EU RISK MANAGEMENT PLAN (RMP)

for

Entyvio® (Vedolizumab)

RMP Version number: 9.0

Date: 13-January-2025

[redacted]

[redacted]

EU Risk Management Plan for Entyvio® (Vedolizumab)

RMP version to be assessed as part of this application:

RMP Version number: 9.0

Data lock point (DLP) for this RMP: 19-November-2024

Date of final sign off: 13-January-2025

Rationale for submitting an updated RMP:

The RMP is being updated to reflect the final data for the subcutaneous (SC) formulation, phase 3 long-term extension, category 3 study MLN0002SC-3030. Additionally, the missing information 'Long term safety' is removed from the list of safety concerns following study completion.

Summary of significant changes in this RMP:

RMP Module:	Significant Changes:
Part I Product Overview	Updated 'Pharmacotherapeutic group', 'ATC code', 'Indication', 'Posology' and 'Important information about its composition' as per the current summary of product characteristics (SmPC).
Part II Safety Specification	
• **Module SI Epidemiology of the indication(s) and target population(s)**	Not applicable
• **Module SII Nonclinical part of the safety specification**	Not applicable
• **Module SIII Clinical trial exposure**	Updated as per the DLP of the RMP.
• **Module SIV Populations not studied in clinical trials**	SIV.3 was updated in alignment with the updated clinical trial exposure data included in Module SIII.
• **Module SV Post-authorisation experience**	Updated exposure data till 31-October-2024
• **Module SVI Additional EU requirements for the safety specification**	Not applicable
• **Module SVII Identified and potential risks**	SVII.2: Added justification for the removal of missing information 'Long term safety'. SVII.3: Updated to 'Not applicable' following removal of missing information
• **Module SVIII Summary of the safety concerns**	Removed missing information 'Long term safety'
Part III Pharmacovigilance plan	MLN0002SC-3030 study was completed therefore, removed as an additional pharmacovigilance activity.

[redacted]

RMP Module:	Significant Changes:
Part IV Plans for post-authorisation efficacy studies	Not applicable
Part V Risk minimisation measures	SV.1: Updated to 'Not applicable' following removal of the missing information 'Long term safety'. SV.3: 'Summary of risk minimisation measures' was updated to 'Not applicable'
Part VI Summary of the risk management plan	• Removed missing information 'Long term safety' from Table II.A List of Important Risks and Missing Information and Table II.B: Summary of important risks. • II.C. Post authorisation Development Plan - Updated following completion of MLN0002SC-3030 study.
Part VII Annexes	Annex 2: Updated MLN0002SC-3030 study status from 'ongoing' to 'completed'. MLN-0002-401 Post Authorisation Safety Study (PASS): Added submission dates of final clinical study report (CSR). Annex 8: Updated to include summary of changes to the risk management plan version 9.0.

Other RMP versions under evaluation:

RMP Version number: Not applicable

Submitted on: Not applicable

Procedure number: Not applicable

[redacted]

Details of the currently approved RMP:

Version number:	8.1
Approved with procedure:	EMEA/H/C/002782/II/0073
Date of approval (EC Decision date):	06-July-2023

Qualified Person for Pharmacovigilance (QPPV) name: Jean-Marie Heim, MD

Please note that e-signature may also be performed by Deputy EU QPPV [redacted], Deputy EU QPPV [redacted], or Deputy EU QPPV [redacted] on behalf of the EU and UK QPPV (i.e. 'per procurationem').

QPPV signature: [redacted] RMP signatures are kept on file.

[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Definition/Description
AE	Adverse Event
ATC code	Anatomical Therapeutic Chemical classification system
AUC	Area Under Curve
CD	Crohn's Disease
CHO	Chinese Hamster Ovary
CSR	Clinical Study Report
CV	Cardiovascular
DLP	Data Lock Point
eCTD	electronic Common Technical Document
EEA	European Economic Area
EMA	European Medicines Agency
EN	Erythema Nodosum
EPAR	European Public Assessment Report
EU	European Union
FAP	Familial Adenomatous Polyposis
GALT	Gut Associated Lymphoid Tissue
GI	Gastrointestinal
GLP	Good Laboratory Practice
HAHA	Human Anti-Human Antibody
IBD	Inflammatory Bowel Disease
IDA	Iron Deficiency Anaemia
IM	Intramuscular
INN	International Non-Proprietary Names
IPAA	Ileal Pouch-Anal Anastomosis
IRR	Infusion-Related Reactions

[redacted]

Abbreviation	Definition/Description
IV	Intravenous
LGD	Low-Grade Dysplasia
MAA	Marketing Authorisation Application
MAdCAM-1	Mucosal Addressin Cell Adhesion Molecule-1
MAH	Marketing Authorisation Holder
NOAEL	No observed Adverse Effect Level
PASS	Post Authorisation Safety Study
PAHA	Primate Antihuman Antibodies
PG	Pyoderma Gangrenosum
PI	Product Information
PML	Progressive Multifocal Leukoencephalopathy
PRAC	Pharmacovigilance Risk Assessment Committee
PSC	Primary Sclerosing Cholangitis
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance (in the European Union)
RAHA	Rabbit Antihuman Antibodies
RMP	Risk Management Plan
RPC	Restorative Proctocolectomy
RSI	Reference Safety Information
SC	Subcutaneous
SmPC	Summary of Product Characteristics
SMR	Standardised Mortality Ratio
TDAR	T-Cell-Dependent Antibody Response
UC	Ulcerative Colitis
UK	United Kingdom
US	United States

[redacted]

Part I: Product(s) Overview

Table Part 1.1 Product Overview

Active substance(s) **(INN or common name)**	Vedolizumab
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, monoclonal antibodies L04AG05
Marketing Authorisation Holder	Takeda Pharma A/S
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Entyvio
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class Vedolizumab is a glycosylated protein (monoclonal antibody).
	Summary of mode of action Vedolizumab is a gut-selective immunosuppressive biologic. It is a humanised monoclonal antibody that binds specifically to the α4β7 integrin, which is preferentially expressed on gut homing T helper lymphocytes. By binding to α4β7 on certain lymphocytes, vedolizumab inhibits adhesion of these cells to mucosal addressin cell adhesion molecule-1 (MAdCAM-1), but not to vascular cell adhesion molecule-1 (VCAM-1). MAdCAM-1 is mainly expressed on gut endothelial cells and plays a critical role in the homing of T lymphocytes to tissues within the gastrointestinal (GI) tract. Vedolizumab does not bind to, nor inhibit function of, the α4β1 and αEβ7 integrins. The α4β7 integrin is expressed on a discrete subset of memory T helper lymphocytes which preferentially migrate into the GI tract and cause inflammation that is characteristic of ulcerative colitis (UC) and Crohn's disease (CD), both of which are chronic, inflammatory, immunologically-mediated conditions of the GI tract. Vedolizumab reduces gastrointestinal inflammation in UC, CD and pouchitis patients.
	Important information about its composition Vedolizumab is a recombinant humanised monoclonal antibody produced in Chinese hamster ovary (CHO) cells. A specific CHO cell line produces humanised IgG1 antibody with variable regions capable of binding human integrin, α4β7. The intravenous (IV) drug products comprises of vedolizumab

[redacted]

	freeze-dried with histidine, arginine, sucrose and polysorbate 80. The SC drug products comprises of vedolizumab with histidine, arginine, citric acid, sodium citrate, polysorbate 80 and water for injection".
Hyperlink to the Product Information (PI)	Refer to eCTD Module 1.3.1 for proposed PI or latest approved PI.
Indication(s) in the EEA	Current: *IV administration: 300 mg powder for concentrate for solution for infusion* *SC administration: 108 mg solution for injection in pre-filled syringe and 108 mg solution for injection in pre-filled pen* *UC* Entyvio is indicated for the treatment of adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist. *CD* Entyvio is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist. *IV administration: 300 mg powder for concentrate for solution for infusion* *Pouchitis* Entyvio is indicated for the treatment of adult patients with moderately to severely active chronic pouchitis, who have undergone proctocolectomy and ileal pouch anal anastomosis for UC and have had an inadequate response with or lost response to antibiotic therapy.
	Proposed: Not applicable
Dosage in the EEA	Current: *IV and SC administration:* UC and CD The recommended dose regimen of IV vedolizumab is 300 mg administered by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter. Patients with Crohn's disease, who have not shown a response may benefit from a dose of IV vedolizumab at week 10. Some patients who have experienced a decrease in their response may benefit from an increase in dosing frequency to IV vedolizumab 300 mg every 4 weeks. The recommended dose regimen of SC vedolizumab as a maintenance treatment, following at least 2 intravenous infusions, is 108 mg administered by subcutaneous injection once every

	2 weeks. The first subcutaneous dose should be administered in place of the next scheduled intravenous dose and every 2 weeks thereafter. *IV administration:* Pouchitis The recommended dose regimen of IV vedolizumab is 300 mg administered by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: *Powder for concentrate for solution for infusion (IV use)* White to off-white lyophilised cake or powder. Each vial contains 300 mg of vedolizumab. After reconstitution, each ml contains 60 mg of vedolizumab. *Solution for injection (SC use)* Colourless to yellow solution. Each pre-filled syringe / pre-filled pen contains 108 mg of vedolizumab in 0.68 ml
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

[redacted]

Part II: Safety specification

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

Ulcerative Colitis (UC)	
Incidence:	Incidence rates vary within geographic regions. The overall annual incidence estimates of UC in Europe range from 0.6-24.3 per 100,000; 0-19.2 per 100,000 in North America; and 0.1-6.3 per 100,000 in Asia and the Middle East [redacted]. UC is a relapsing and remitting disease and it is estimated that approximately 50% of patients will have inadequate response with, lost response to, or become intolerant to either conventional therapy or a TNFα antagonist at some point during their lifetime. This would mean an estimated incidence of UC in the target population in Europe is approximately 0.3-12.15 per 100,000 persons.
Prevalence:	Prevalence can vary within geographic regions. The prevalence estimates of UC in Europe range from 4.9-505 per 100,000; 37.5-248.5 per 100,000 in North America; and 4.9-168.3 per 100,000 in Asia and the Middle East [redacted].
Demographics of the target population in the indication:	AGE: The peak age of occurrence for UC is between 30 and 40 years of age; however, some studies have reported a second peak occurring between 60 and 70 years of age[redacted]. SEX: UC has been shown to occur slightly more frequently in men (~60%) as compared to women[redacted]. RACE/ETHNICITY: Few studies have evaluated race/ethnicity differences in inflammatory bowel disease (IBD); of those that have, the greatest incidence has been observed in Caucasian and Jewish people[redacted]. It has also been shown that the incidence of IBD in Hispanic and Asian people has been increasing [redacted], and interestingly people emigrating from low prevalence IBD areas (e.g., Asia) to high prevalence countries (e.g., England) are at increased risk for developing IBD, especially among first-generation children [redacted]. For UC, South Asian (SA) and Caucasian (or Malay in one study) groups were compared in 6 studies, including 4 in the United Kingdom (UK) and one in Malaysia and a further study in Canada which was limited to a paediatric population. In all 6 studies there were more SA with pan-colonic disease than Caucasians [redacted]. Also, African-Americans were compared to Caucasians in 6 studies, of which 2 were paediatric. Four studies described a higher proportion of African-Americans having disease limited to the rectum. Hispanics were compared with Caucasians in 4 studies. In the Hispanic group, 2 studies showed no difference in disease location for UC, another significantly less proctitis, with a fourth study demonstrating a significantly increased risk of pan-colitis and higher colectomy rate (32.3% vs 15.8%) [redacted]. GEOGRAPHIC HETEROGENEITY: In Europe, the highest incidence of UC occurs in northern countries as compared to southern countries. This pattern has also been shown in North America [redacted].
Risk factors for the disease:	A family history of UC or CD increases the risk for developing UC. Appendicectomy for proven appendicitis before adulthood, and smoking, reduce the risk and severity of UC. Smoking cessation may predispose to UC. Non-selective non-steroidal anti-inflammatory drugs (NSAIDs) may

[redacted]

Ulcerative Colitis (UC)	
	exacerbate the disease [redacted].
The main existing treatment options:	Conventional pharmacologic treatments for UC include 5-aminosalicylates (5-ASAs), corticosteroids, and immunomodulators (thiopurines such as azathioprine and 6-mercaptopurine, along with methotrexate). For patients who have an inadequate response to conventional therapies, monoclonal antibodies against TNFα, such as infliximab and adalimumab, have substantially improved the care of patients with IBD by inducing and maintaining remission and decreasing the need for hospitalisations and surgeries [redacted]. However, the effectiveness of TNFα antagonists is limited, with treatment failure at the end of the first year of therapy in roughly two-thirds of patients in controlled clinical trials [redacted]. Furthermore, studies have demonstrated that after the failure of one TNFα antagonist, there is a lower likelihood of response to a second TNFα antagonist[redacted].
Natural history of the indicated condition in the population, including mortality and morbidity:	In a population-based inception cohort meta-analysis study of overall and cause-specific mortality among patients with UC overall mortality was not increased as compared to the general population (pooled Standardised Mortality Ratio (SMR) 1.1, 95% confidence interval (CI) 0.9-1.2 [redacted]. As compared to the general population, increased mortality was observed in Scandinavian studies (SMR 1.2, 95% CI 1.1-1.4) and among UC patients with more extensive colitis (SMR 1.2, 95% CI 1.0-1.5) [redacted]. Significant increases in the following cause-specific mortality in patients with UC compared with the general population were also observed: pulmonary embolism (SMR 4.0, 95% CI 1.5-8.7); respiratory diseases (SMR 1.6, 95% CI 1.3-2.0); pneumonia (SMR 3.1, 95% CI 2.0-4.6); gastrointestinal and liver diseases (SMR 2.5, 95% CI 1.9-3.2); and non-alcoholic liver diseases (SMR 4.0, 95% CI 2.5-6.5).
Important co-morbidities:	Several important co-morbidities and extra-intestinal manifestations are presented below. <u>Anaemia</u> Anaemia is common in UC, found in 21% of all patients. The most common forms of anaemia in UC are iron deficiency anaemia [redacted], anaemia of chronic disease, and a combination of both. Vitamin B12 or folate deficiency, haemolytic anaemia, and drug-induced anaemia are less prevalent forms [redacted]. <u>Arthropathy</u> Joint involvement is another most common extra-intestinal manifestation in UC, occurring in approximately 20% of all patients[redacted]. <u>Ocular manifestations</u> Episcleritis generally parallels UC activity. It can be self-limiting and usually responds to topical corticosteroids and NSAIDs prescribed alongside treatment of the underlying UC. When related to UC, uveitis is frequently bilateral, has an insidious onset, and is long lasting [redacted]. <u>Hepatobiliary disease</u> Concomitant primary sclerosing cholangitis (PSC) is an important hepatobiliary condition in patients with UC. However, peri-cholangitis, steatosis, chronic hepatitis, cirrhosis, and gallstone formation are also over-represented in these patients. The frequency of PSC in IBD is not well understood; however, it has been estimated that between 2.5% to

[redacted]

Ulcerative Colitis (UC)	
	7.5% of patients who present with UC have, or will have, PSC [redacted]. Additionally, it has been observed that PSC is more common in patients with UC than with CD [redacted]. Primary sclerosing cholangitis is a major risk factor for both cholangiocarcinoma and colon cancer[redacted]. <u>Metabolic Bone Disease (Osteopenia and Osteoporosis)</u> The prevalence of bone disease in patients with IBD has been observed in the ranges of 5% [redacted] to 78% [redacted]. Specifically, it has been observed that the range of prevalence of osteopenia in IBD is 22% to 77% [redacted], and the range of prevalence of osteoporosis in IBD is 17% to 44%[redacted]. The wide variation in study findings may be attributed to different definitions of bone disease, the technology used, the site assessed, and heterogeneity in the IBD population. It's been indicated that loss of bone density is more pronounced in CD compared with UC[redacted]. <u>Cutaneous manifestations</u> Erythema nodosum (EN) and pyoderma gangrenosum (PG) are described as the most common cutaneous manifestations of IBD. The prevalence of EN and pyoderma gangrenosum in patients diagnosed with IBD is 3-8% and 1-2%, respectively [redacted]. Erythema nodosum Erythema nodosum usually affects the extensor surfaces of the lower extremities, particularly the anterior tibial areas, and has a symmetrical distribution. It is closely related to disease activity, and its treatment is based on that of the underlying UC[redacted]. Pyoderma gangrenosum Pyoderma gangrenosum lesions are often preceded by trauma, a phenomenon known as pathergy. They most frequently occur on the shins and adjacent to postsurgical stomas [redacted]. <u>Opportunistic infections</u> Ulcerative colitis patients at risk of opportunistic infections are those treated with immunomodulators, especially in combination, and those with malnutrition [redacted]. <u>Colorectal cancer</u> The risk of colorectal cancer in UC is increased compared with the general population. Risk is associated with disease duration, extent, and more severe or persistent inflammatory activity [redacted]. <u>Obesity</u> An increasing prevalence of obesity in patients with IBD has been observed recently, whereas in the past obese IBD patients were the exception. In a recent study by Steed et al [redacted], it was reported that between 15% and 20%, and possibly up to 40%, of patients with IBD are overweight. Although there is no direct relationship shown between obesity and adverse outcomes in patients with IBD, obesity in the general population has been shown to be related to unfavourable outcomes such as colonic adenomas, surgical complications, and increased cardiovascular (CV) and thrombotic events and disease.

[redacted]

Ulcerative Colitis (UC)	
	Cardiovascular Comorbidity In the general population, CV disease is the main cause of death in developed countries, and its prevalence increases with age. Patients with IBD may also experience CV co-morbidities. In particular, therapies for the management and treatment of IBD have been shown to have deleterious CV effects. Specifically, glucocorticoids have been associated with the following adverse CV effects: hypertension, hyperglycaemia, hyperinsulinemia, and hyperlipidaemia [redacted]. Venous thromboembolism Patients with IBD are at increased risk for venous thromboembolism. The prevalence of venous thromboembolism in IBD ranges between 1.2 and 6.7% in clinical studies. Deep venous thromboses of the leg and pulmonary emboli (PE) are the most common thromboembolic manifestations, but unusual sites of venous thromboembolism, such as cerebrovascular, portal, mesenteric and retinal veins, have also been described. Evidence from the population-based cohort study shows an incidence rate of deep venous thromboses of 30.7 per 10,000 person-years in IBD patients (30.0 for UC patients) and 14.9 per 10,000 person-years for PE in the entire IBD population (19.8 for UC) [redacted].

Crohn's Disease (CD)	
Incidence:	Incidence rates can vary within geographic regions. The overall incidence estimates for CD in Europe range from 0.3-12.7 per 100,000; 0-20.2 per 100,000 in North America; and 0.04-5.0 per 100,000 in Asia and the Middle East [redacted]. CD is a relapsing and remitting disease and it is estimated that approximately 50% of patients will have inadequate response with, lost response to, or become intolerant to either conventional therapy or a TNFα antagonist at some point during their lifetime. This would mean an estimated incidence of CD in the target population in Europe is approximately 0.15-6.35 per 100,000 persons.
Prevalence:	Prevalence can vary within geographic regions. The prevalence estimates for CD in Europe range from 0.6-322 per 100,000; 16.7-318.5 per 100,000 in North America; and 0.88-67.9 per 100,000 in Asia and the Middle East [redacted].
Demographics of the target population in the indication:	AGE: The peak age of occurrence for CD is between 20 and 30 years of age; however, some studies have reported a second peak occurring between 60 and 70 years of age [redacted]. SEX: CD occurs on average 20-30% more frequently in women than in men, particularly in high-incidence areas. RACE/ETHNICITY: Few studies have evaluated race/ethnicity differences in IBD; of those that have, the greatest incidence has been observed in Caucasian and Jewish people [redacted]. It has also been shown that the incidence of IBD in Hispanic and Asian people has been increasing [redacted], and interestingly, people emigrating from low prevalence IBD areas (e.g., Asia) to high-prevalence countries (e.g., England) are at increased risk for developing IBD, especially among first-generation children [redacted]. For CD, SA group was compared with Caucasians in 4 studies, and all

[redacted]

Crohn's Disease (CD)	
	reported on both location and disease behaviour. Two were from the UK, one from the United States (US), and one from Canada. Two studies (UK and Canada) showed SA significantly more likely to have colonic disease. The Canadian study also showed that SA had less ileal involvement. One UK study showed SA had less stricturing (B2) and less non-penetrating disease (B3), but this was not significant. In contrast, perianal disease was significantly more common in SA compared with Caucasians in 2 studies [redacted]. African-American and Caucasian groups were compared for disease location in 8 studies, all from the US, 3 of which were in paediatric populations. African-Americans showed significantly less ileal disease (L1) in several studies. African-Americans showed more significantly more structuring (B2) and penetrating disease (B3) in one study and perianal disease in 2 studies [redacted]. Hispanics showed significantly lower rates for ileal disease and higher rate of colonic disease compared with Caucasians in one study population of 697 cases. Perianal presentation was significantly more frequent in Hispanics in only 2/4 studies but these studies represented 92% of the studied cohorts (7,376/7,974)[redacted]. GEOGRAPHIC HETEROGENEITY: In North America, the highest incidences of CD occur in Canada and in the northern US as compared to the southern part of the continent [redacted]. In Europe, the highest incidence of CD occurs in northern countries as compared to southern countries.
Risk factors for the disease:	Well proven risk factors for CD include smoking, family history of IBD, and recent infectious gastroenteritis [redacted].
The main existing treatment options:	Conventional pharmacologic treatments for CD include 5-ASAs, corticosteroids, and immunomodulators (thiopurines such as azathioprine and 6-mercaptopurine, along with methotrexate). For patients who have an inadequate response to conventional therapies, monoclonal antibodies against TNFα, such as infliximab and adalimumab, have substantially improved the care of patients with IBD by inducing and maintaining remission and decreasing the need for hospitalisations and surgeries [redacted]. However, the effectiveness of TNFα antagonists is limited, with treatment failure at the end of the first year of therapy in roughly two-thirds of patients in controlled clinical trials [redacted]. Furthermore, studies have demonstrated that after the failure of one TNFα antagonist, there is a lower likelihood of response to a second TNFα antagonist [redacted].
Natural history of the indicated condition in the population, including mortality and morbidity:	In a population-based meta-analysis study of overall and cause-specific mortality among patients with CD, overall mortality was slightly but significantly higher (pooled SMR 1.39, 95% CI 1.3-1.49) than in the general population, primarily explained by deaths from gastrointestinal, respiratory, and genitourinary diseases [redacted]. More specifically, a significantly increased risk of death from cancer (SMR 1.50 95% CI 1.18-1.92), in particular of pulmonary cancer (SMR 2.72, 95% CI 1.35-5.45), as well as chronic obstructive pulmonary disease (COPD) (SMR 2.55, 95% CI 1.19-5.47), gastrointestinal diseases (SMR 6.76, 95% CI 4.37-10.45), and genitourinary diseases (SMR 3.28, 95% CI 1.69-6.35) were observed [redacted]. The authors suggest that smoking may explain some of the increased mortality from respiratory cancers, COPD, and genitourinary cancers, although more research is needed[redacted].

[redacted]

Crohn's Disease (CD)	
Important co-morbidities:	Several important co-morbidities and extra-intestinal manifestations are presented below. Arthropathy Peripheral arthropathy This arthropathy is observed in 4–17% of patients with CD and may be present in around 15% at the time of diagnosis. Type II is a polyarticular arthritis mainly affecting the small joints of the hand but independent of CD activity and is observed in about 2-4% of patients with CD [redacted]. Axial arthropathy Axial arthropathy includes sacroiliitis and spondylitis. Irrespective of the presence of inflammatory back pain, isolated radiographic sacroiliitis has been found in 25–50% of patients with CD[redacted]. Metabolic bone disease Low bone mass and osteoporosis are common in both male and female patients with CD (20–50%). Contributing factors include chronic inflammation, corticosteroid treatment, extensive small bowel disease or resection, age, smoking, low physical activity and nutritional deficiencies [redacted]. Cardiopulmonary disease Cardiac involvement is considered rare and many times is subclinical. While increased risk of venous thromboembolic events is now well established, the risk of CV disease has been debated. Pulmonary disease represents a rare extra-intestinal manifestation of IBD, but its true prevalence is unknown. Respiratory symptoms may be present in >50% of IBD patients, and although these are often mild, attributed to smoking or ignored, more recent studies suggested a possible association between airways disease and CD, for example asthma in population-based studies [redacted]. Hepatobiliary disease Liver test abnormalities are common in IBD although more often associated with hepatobiliary disease in UC than in CD, and are associated with a small but significant reduction in survival. PSC is less common in CD than in UC. However, peri-cholangitis, steatosis, chronic hepatitis, cirrhosis and gallstone formation are also over-represented. PSC is a major risk factor for cholangiocarcinoma and colon cancer [redacted]. Cutaneous manifestations *Erythema nodosum* Erythema nodosum is usually readily recognised. Data indicates that prevalence of EN in IBD and CD, respectively, ranged from 4.2 to 7.5% and seems to be higher in CD than in UC. *Pyoderma gangrenosum* In recent publications, 0.6–2.1% of CD patients developed pyoderma gangrenosum [redacted]. Venous thromboembolism Patients with IBD are at increased risk for venous thromboembolism. The

[redacted]

Crohn's Disease (CD)	
	prevalence of venous thromboembolism in IBD ranges between 1.2 and 6.7% in clinical studies. Deep venous thromboses of the leg and PE are the most common thromboembolic manifestations, but unusual sites of venous thromboembolism, such as cerebrovascular, portal, mesenteric and retinal veins, have also been described. Evidence from the population-based cohort study indicates an incidence rate of deep venous thromboses of 30.7 per 10,000 person-years in IBD patients (31.4 for CD patients) and 14.9 per 10,000 person-years for PE in the entire IBD population (10.3 for CD) [redacted].

Pouchitis	
Incidence:	Pouchitis is a common complication of ileal pouch-anal anastomosis (IPAA), a surgical option offered to patients with ulcerative colitis (UC) and familial adenomatous polyposis (FAP) [redacted]. Several studies have shown that the incidence and cumulative risk for the first attack of pouchitis is highest during the first year after surgery, after which the incidence and risk levels off. The cumulative frequency rates of pouchitis 10 years after an IPAA surgery are reported to range from 23% to 60%[redacted]. The estimated incidence within 12 months after ileostomy was as high as 40% in a European study [redacted]. It is also estimated that approximately 50% of patients who have undergone IPAA surgery for UC will develop at least one episode of pouchitis[redacted].
Prevalence:	Prevalence of pouchitis is not very well described in the literature; however, it has been estimated that the total number of patients with pouchitis in the US will eventually reach 30,000–45,000, or a prevalence of 12–18/100,000 [redacted]. The European Medicine Agency (EMA) cited the prevalence of approximately 2.2 in 10,000 people in the European Union (EU). This is equivalent to a total of around 114,000 people; the number of patients affected by the condition is estimated and assessed on the basis of data from the EU (27 from 2020), UK, Norway, Iceland and Liechtenstein [redacted]. Pouchitis is more commonly seen in patients with UC than in patients with FAP. In a systematic review and meta-analysis of 18117 patients with UC and 860 patients with FAP who underwent IPAA, the prevalence of pouchitis was 32% in UC and 6% in FAP respectively [redacted].
Demographics of the target population in the indication:	Most large series on IPAA report a mean age between 30 and 35 years. Given the complexity of IPAA and its possible morbidities such as pelvic sepsis, anastomotic leakage, increased stool frequency, pouchitis, faecal incontinence, evacuation disorders, and pouch failure, many surgeons have avoided its use in patients older than 50 years. However, evidence now indicate that IPAA has been performed increasingly on a larger population of patients older than 50 years. In one study conducted in the US, pouchitis rates were significantly higher in patients who were between 46 and 55 years compared with the patients 45 years or younger. Men and women had similar rates for the development of pouchitis [redacted]. Patients who have an IPAA typically have 4 to 8 bowel movements per

[redacted]

Pouchitis	
	day. Patients with pouchitis are characterized by increased stool frequency and liquidity, abdominal cramping, urgency and tenesmus, and occasionally rectal bleeding or fever. Faecal incontinence is not uncommon after IPAA, and is more common in the presence of pouchitis [redacted]. In addition, patients with severe pouchitis occasionally present with fever, dehydration, malnutrition which may require hospitalization. Patients may have predominant symptoms such as arthralgia and uveitis [redacted].
Risk factors for the disease:	Although the precise pathogenesis of pouchitis remains unknown, several risk factors for pouchitis have been identified. It's been indicated that gut microbiota and mucosal immunity, genetic, vascular, and luminal factors such as NSAIDs are likely to contribute to the initiation, exacerbation, and progression of pouchitis. Pouchitis occurs more commonly in patients with restorative proctocolectomy with underlying IBD than in those with FAP [redacted] suggesting the contribution of genetic and/systemic factors to its pathogenesis [redacted]. Also, immunogenetic studies showed that genetic polymorphisms such as those of IL-1–receptor antagonist, nucleotide-binding oligomerization domain containing 2/caspase recruitment domain family, member 15 (NOD2/ CARD15), or a combined carriership of Toll-like receptor 9-1237C and CD14-260T alleles, were associated with the risk for chronic Pouchitis [redacted]. Gastrointestinal, systemic, or environmental risk factors reported to be associated with pouchitis include extensive UC, the presence of backwash ileitis, precolectomy thrombocytosis, the presence of concurrent PSC or other immune-mediated disorders, the regular use of NSAIDs and ischemia[redacted]. Studies on smoking and pouchitis are conflicting. One study found that smoking increased the risk of developing acute pouchitis (episodes that were antibiotic responsive occurring at least 4 months apart) (OR 2.3 [95% CI: 1.1–5.3]) but reduced the risk for chronic pouchitis (antibiotic dependent and antibiotic refractory) (OR 0.2 [95% CI: 0.05–0.74]). Evidence on the risk of pouchitis for never smokers is conflicting. Some studies demonstrate a higher risk for, pouchitis, but these findings were unable to be replicated in subsequent studies [redacted]. Overall, several risk factors for pouchitis have been identified including extraintestinal manifestations of IBD, autoimmune disorder(s), severity of disease, serologic markers (serum IgG4, autoantibodies to bacterial antigens, p-ANCA, and anti-CBir1 flagellin antibody), genetic markers (NOD2 mutation), smoking, and certain dietary factors (i.e., the decreased consumption of antioxidants by patients with pouchitis may expose them to the effects of inflammatory and oxidative stress and contribute to the manifestation of pouchitis [redacted].
The main existing treatment options:	There are no pharmacological treatments approved for pouchitis in the EU, in the UK or in the US. Therapies used for pouchitis include antibiotics (drugs for bacterial infections) - used as first line, budesonide enemas (a steroid drug), probiotics (helpful bacteria), biologic agents that target tumor necrosis factor, glutamine suppositories (an amino acid), butyrate suppositories (short chain fatty acid), bismuth enemas (diarrhoea medication), allopurinol (a purine analogue drug), and tinidazole (an anti-parasitic drug) [redacted].

[redacted]

Pouchitis	
	Although the majority of patients with pouchitis respond favorably to antibiotic therapy, particularly in the initial stages of disease, some patients develop pouchitis refractory to routine antibiotic treatment. Traditional IBD treatments such as corticosteroids, biologics, and small molecule drugs can be considered for patients with chronic pouchitis who cannot take or are refractory to antibiotics [redacted]. Besides medical treatment, physicians may also recommend a low-carbohydrate, low-fiber and high protein diet to help relieve symptoms of chronic pouchitis [redacted]. Antidiarrheal agents may be used to treat frequent or loose bowel movements.
Natural history of the indicated condition in the population, including mortality and morbidity:	Proctocolectomy with IPAA is the procedure of choice for most patients with UC who require colectomy for medically refractory disease or a complication such as dysplasia. It is estimated that 25–30% of patients with ulcerative colitis eventually require colectomy, and the majority of these patients have an IPAA. Pouchitis is an idiopathic chronic inflammatory condition that may occur in the ileal pouch in up to 60% of patients after IPAA for UC. Some studies report that most cases of pouchitis occur within the first few years after IPAA, while others show that risk may continue to increase with longer follow-up. In contrast, prevalence of pouchitis in patients who have IPAA for FAP is lower compared to that in patients with UC [redacted]. Patients with pouchitis can be classified according to disease activity, symptom duration, disease pattern or response to antibiotics. Disease activity can be classified as remission or mildly, moderately, or severely active based primarily on symptoms. Duration can be classified as acute (<4 weeks) or chronic (>=4 weeks). Disease pattern can be classified as infrequent (1–2 acute episodes), relapsing (>=3 acute episodes) or continuous. Relapsing pouchitis is also considered a form of chronic pouchitis, even if the symptoms do not last for 4 weeks on therapy[redacted]. Mortality is not very well described in published literature. However, research in a cohort of 820 patients with IPAA for UC at the Cleveland Pouchitis Clinic from 2002-2008 identified a total of 7 deaths (0.85%) with an average age at death of 59.7 years old and an average pouch duration of 8 years. Of these deceased patients, 4 patients had developed pouchitis after IPAA. Two patients had mortality related to chronic pouch inflammation: one patient died of stroke following pouch revision for cancer, the other died from *Clostridium difficile* infection following treatment for refractory pouchitis [redacted]. Also, in a cohort study of 1097 UC patients with IPAA at the Mayo Medical Center in Minnesota between 1981 and 1993, 6 patients with PSC died of cholangiocarcinoma, liver cirrhosis, and metastatic colon cancer. Of them, 3 patients developed pouchitis after IPAA[redacted]. A retrospective analysis using the National Readmission Database found that readmissions in pouchitis patients are frequent. The study identified 1538 pouchitis patients who were discharged alive from Jan 2013 to Dec 2013. Among them, 10.2% were readmitted within 30 days of discharge. There were 629 patients who died with a diagnosis of pouchitis during the study year, and only 1 of them died in the hospital[redacted].
Important co-morbidities:	Pouchitis almost exclusively occurs in patients with underlying UC[redacted]. However, there are not many specific studies describing the range of comorbidities in patients with pouchitis. Considering pouchitis occurs in

[redacted]

Pouchitis	
	patients with UC, these patients may present with a number of similar co-morbidities and extra-intestinal manifestations that are present in patients with UC: Anaemia Anaemia is common in UC, found in 21% of all patients. The most common forms of anaemia in UC are iron deficiency anaemia (IDA), anaemia of chronic disease, and a combination of both. Vitamin B12 or folate deficiency, haemolytic anaemia, and drug-induced anaemia are less prevalent forms [redacted]. In Finland, a hospital-based study based on data from 48 UC patients aged 27-75 years who underwent restorative proctocolectomy (RPC) between 1985 and 1990 found that 20.8% of the patients (n=10) had been diagnosed with anaemia over a median follow-up time of 9.8 years. Of the 10 patients, 8 had severe or chronic pouchitis (P=0.02) which predisposed to anaemia resulting from recurrent bleeding from the pelvic pouch [redacted]. Another longitudinal study using data from a Swedish hospital registry in 91 patients aged 14-57 years who underwent RPC between 1980 and 1990 reported that iron-deficiency anaemia was diagnosed in 7, 5, and 4 patients with recurrent bleeding from the pelvic reservoir and chronic pouchitis at 1 and 3 years and at a mean of 13.5 years after loop ileostomy, respectively [redacted]. Arthropathy Joint involvement is another most common extra-intestinal manifestation in UC, occurring in approximately 20% of all patients [redacted]. Ocular manifestations Episcleritis generally parallels UC activity. It can be self-limiting and usually responds to topical corticosteroids and NSAIDs prescribed alongside treatment of the underlying UC. When related to UC, uveitis is frequently bilateral, has an insidious onset, and is long lasting [redacted]. Hepatobiliary disease Concomitant PSC is an important hepatobiliary condition in patients with UC. However, peri-cholangitis, steatosis, chronic hepatitis, cirrhosis, and gallstone formation are also over-represented in these patients. The frequency of PSC in IBD is not well understood; however, it has been estimated that between 2.5% to 7.5% of patients who present with UC have, or will have, PSC [redacted]. Additionally, it has been observed that PSC is more common in patients with UC than with CD [redacted]. Erythema nodosum Erythema nodosum usually affects the extensor surfaces of the lower extremities, particularly the anterior tibial areas, and has a symmetrical distribution. It is closely related to disease activity, and its treatment is based on that of the underlying UC [redacted]. Opportunistic infections Ulcerative colitis patients at risk of opportunistic infections are those treated with immunomodulators, especially in combination, and those with malnutrition [redacted].

[redacted]

Pouchitis	
	Colorectal cancer The risk of colorectal cancer in UC is increased compared with the general population. Risk is associated with disease duration, extent, and more severe or persistent inflammatory activity [redacted]. Several studies describing additional comorbidities are presented below. Pouch failure A longitudinal study using data on 2491 patients undergoing primary restorative proctocolectomy (RPC) between 1976 and 2006 from the UK National Ileal Pouch Registry found that, over a median follow-up time of 54 months, 327 patients developed pouchitis after primary RPC; 192 patients had incidence of pouch failure, defined as the ileal pouch excision or indefinite diversion. Of the 94 patients with information on cause of failure available, 9 failures (9.6%) were due to pouchitis [redacted]. A recent study in a Japanese cohort of 1347 adults and 90 paediatric patients (≤ 8 years; 51 boys and 39 girls) with UC who underwent RPC with IPAA showed that pouchitis was significantly associated with elevated risk for development of pouch failure in paediatric patients (hazard ratio=19.3; 95% CI%: 4.1-91.1) without sex differences[redacted]. Pouch polyps Among a cohort of 1094 patients with restorative protocolectomy and IPAA for IBD recruited from the Cleveland Foundation Pouchitis Clinic (2002-2010), those with chronic pouch inflammatory changes (defined as chronic antibiotic-refractory pouchitis, CD of the pouch, or cuffitis) had a 2-fold increased risk for developing pouch polyps (odds ratio=2.26, 95% CI: 1.35-3.79). On histology, 93 patients (96.9%) had inflammatory-type polyps, 2 (2.1%) were indefinite for dysplasia, and 1 (1.0%) had low-grade dysplasia (LGD) in subsequent biopsy [redacted]. Skin lesions (particularly pyoderma gangrenosum), arthritis, and eye problems (particularly uveitis) In the United States, a study of 734 patients aged 32 years on average who underwent IPAA at Mayo Clinic between 1981 and 1988 showed that, over a mean follow-up period of 41 months, the 12 of these 734 patients had the onset or worsening of extraintestinal manifestations (EIMs)-like iridocyclitis (i.e. uveitis and episcleritis), skin lesions (i.e. pyoderma gangrenosum, EN, and polyarteritis nodosum), or seronegative arthritis (including arthritis, ankylosing spondylitis, and sacroileitis), concomitant with the incidence of pouchitis. Of them, 7 patients had their EIMs quiescent when pouchitis was treated or recurrent with episodes of pouchitis [redacted]. A few cases of pyoderma gangrenosum (one case concomitant with arthritis) have been reported among patients with chronic or acute pouchitis aged 14-43 years in UK, Greece, and Hungary [redacted]. In Israel, 4 cases of seronegative arthritis accompanied by enthesopathy (n=2) and by sacroiliitis (n=2) have been reported in patients with IPAA for UC and aged 25-57 years. All of them had active pouchitis occurring before or at the same time as appearance of arthritis[redacted].

[redacted]

Part II: Module SII - Nonclinical part of the safety specification

Key safety findings from nonclinical studies and relevance to human usage:

Key Safety Findings	Relevance to human usage
Toxicity: In single and repeat-dose toxicology studies, doses of up to 100 mg/kg (46 and 18 times that at the human clinical dose of 300 mg, in terms of C_{max} and area under curve [AUC], respectively) were well tolerated, with no adverse effects. Minimal to mild atrophy of Peyer's patches (i.e., gut-associated lymphoid tissue [GALT]) was observed that was consistent with observations in knock-out mice in which the β7 chain was not expressed. This pharmacologic effect may be explained by the decreased trafficking of peripheral lymphocytes into GALT as a result of antagonism of the α4β7/MAdCAM-1 pathway by vedolizumab. In addition, in these good laboratory practice (GLP)-compliant toxicology studies, a similar effect was not observed in other lymphoid organs, and there was no evidence of systemic immunosuppression.	These results illustrate that the specific antagonism of the $\alpha4\beta7$/MAdCAM-1 pathway by vedolizumab elicits a gut-selective pharmacologic profile. This is relevant to human usage in terms of reduced potential for systemic immunosuppression and adverse events (AEs) subsequent to systemic immunosuppression.
Vedolizumab had little or no carcinogenic potential because it did not affect cellular proliferation of haematologic tumours that express the $\alpha4\beta7$ integrin in vitro. In addition, it did not affect cell proliferation and/or cell death in tissues during repeat-dose toxicology investigations in vivo, and there was no evidence of systemic immunosuppression.	Nonclinical studies demonstrated no evidence of risk carcinogenicity to humans. The carcinogenicity potential of vedolizumab has been monitored in the clinical development program and is being further monitored during the post-authorisation period.
The need for a dedicated Segment I fertility study is obviated by the lack of cross-reactivity of the vedolizumab target in human reproductive tissues, and due to the absence of any vedolizumab-induced gross or microscopic alterations upon thorough evaluations of all reproductive tissues from repeat-dose toxicology studies, the absence of a pharmacologically responsive rodent species, and the finding of normal fertility in β_7 integrin homozygous null (itgb7$^{-/-}$) mice. In a GLP-compliant embryo-foetal development study conducted in gravid New Zealand white rabbits, single IV infusions of vedolizumab administered on gestation Day 7 at doses up to 100 mg/kg were well tolerated, with no evidence of maternal or embryo-foetal effects. In a GLP-compliant Segment II/III study in 12 gravid, sexually mature, at least 3-year-old cynomolgus monkeys dosed every 2 weeks from gestation days 20 to 140, with monitoring of	Although no safety signal was seen in animals, the potential effects of vedolizumab on human fertility have not been studied in the clinical development program. Male and female contraception have been recommended for at least 4 months after the last dose of vedolizumab in clinical trials.

Key Safety Findings	Relevance to human usage
toxicity effects in their infants up to 6 months of age, the no observed adverse effect level (NOAEL) for prenatal and postnatal development was 100 mg/kg, the highest dose evaluated.	
Specialised assessments for clinical infections, systemic immunotoxicity (T-cell-dependent antibody response [TDAR], peripheral blood lymphocyte subset phenotyping, and natural killer [NK] cell activity) were included in the 13- and 26-week cynomolgus monkey toxicology study at doses up to 100 mg/kg administered IV every 2 weeks. Vedolizumab had no effect on antigen stimulus response, NK cell activity, or lymphocyte immunophenotype or lymphocyte numbers (evaluated in the 26-week study only). Drug-related clinical infections were not observed. The 3-month, GLP-compliant, repeat-dose toxicology study conducted with vedolizumab in New Zealand white rabbits revealed no adverse effects on clinical status, body weight, laboratory tests, or physical, indirect ophthalmic, and complete anatomic pathology examinations upon repeat dosing at 30 or 100 mg/kg IV, administered once every 2 weeks. This study confirmed continuous target saturation through 3 months of dosing in most rabbits at the NOAEL of 100 mg/kg, the highest dose tested. Similar findings and NOAEL were observed in the 13- and 26-week repeat-dose toxicology studies in cynomolgus monkeys, under conditions of target saturation for the duration of the study.	Investigations of the potential for systemic immunosuppressive effects of vedolizumab have been performed in the clinical development program as well as further mechanistic studies and Study C13013, a vaccine study.
Rabbit and primate antihuman antibodies (RAHA and PAHA) to vedolizumab have been evaluated in these investigations. Only sporadic, mild, and transient infusion reactions were noted. The infusion reactions/immunogenicity noted are not considered predictive of effects in humans because infusion reactions are to be expected in nonhuman species given humanised antibodies. When vedolizumab was administered subcutaneously (SC) and intramuscularly (IM) to New Zealand white rabbits, local injection site reactions were of low severity and consistent with injection site trauma.	Immunogenicity has been evaluated in the clinical development program. Development of human anti-human antibody (HAHA) in patients who received at least 1 dose of vedolizumab was approximately 4%. Serious infusion-related reactions (IRRs), the consequence of immunogenicity, have been evaluated in the clinical trials.
Safety pharmacology: Vedolizumab did not adversely affect the CV, gastrointestinal, renal, pulmonary, and central nervous systems based on functional assessments and microscopic evaluations of tissues from 13- and 26-week toxicology studies and the results from a single-dose,	Specific cardiac function parameters were not included among exclusion criteria in vedolizumab clinical trials. Cardiac events were no more common among vedolizumab-treated patients compared to placebo-treated controls and were related to pre-existing cardiac conditions, such as coronary artery disease.

Key Safety Findings	**Relevance to human usage**
GLP-compliant, CV safety pharmacology study in cynomolgus monkeys. Nonclinical studies show no evidence of cardiotoxic effects of vedolizumab.	The clinical QT study, C13009, did not demonstrate any specific QT abnormalities.
Other toxicity-related information or data: None.	Not applicable.

[redacted]

Part II: Module SIII - Clinical trial exposure

Table SIII.1.1 Duration of exposure in studies across all indications

Cumulative for all indications (person time):		
Duration of exposure (Months)	**Patients n (%)**	**Person time (Months)**
≥1 Dose	3,867 (100)	146,150.6
≥6	3,406 (88.1)	143,840.1
≥12	2,825 (73.1)	138,507.6
≥18	2,295 (59.3)	130,583.0
≥24	2,002 (51.8)	124,456.0
≥30	1,816 (47.0)	119,429.1
≥36	1,669 (43.2)	114,580.6
≥48	1,407 (36.4)	103,429.7
≥60	1107 (28.6)	87,216.7
≥72	778 (20.1)	65,411.2
≥84	311 (8.0)	28,943.3
≥96	70 (1.8)	7,622.5

Data available up to 19-November-2024.
Included in the analysis are the patients and their time on Vedolizumab only.
(Vedolizumab studies C13006, C13007, C13008, C13011, Vedolizumab-4004, MLN0002SC-3027, MLN0002SC-3030, and MLN0002SC-3031).
Exposure duration for all patients on drug is (last dose date - first dose date + 127).

Table SIII.1.2 Duration of exposure in ulcerative colitis studies

Person time per indication:		
Ulcerative Colitis		
Duration of exposure (Months)	**Patients n (%)**	**Person time (Months)**
≥1 Dose	1,460 (100)	61,629.4
≥6	1,325 (90.8)	60,953.2
≥12	1,150 (78.8)	59,350.8

[redacted]

Person time per indication:		
Ulcerative Colitis		
Duration of exposure (Months)	**Patients n (%)**	**Person time (Months)**
≥18	953 (65.3)	56,388.1
≥24	832 (57.0)	53,866.8
≥30	762 (52.2)	51,977.6
≥36	708 (48.5)	50,180.8
≥48	608 (41.6)	45,966.6
≥60	489 (33.5)	39,578.0
≥72	383 (26.2)	32,496.6
≥84	165 (11.3)	15,473.6
≥96	41 (2.8)	4,524.2

Data available up to 19-November-2024.
Included in the analysis are the patients and their time on Vedolizumab only.
Vedolizumab studies C13006, C13008, MLN0002SC-3027, and MLN0002SC-3030
Exposure duration for all patients is (last dose date - first dose date + 127).

Table SIII.1.3 Duration of exposure in Crohn's disease studies

Person time per indication:		
Crohn's Disease		
Duration of exposure (Months)	**Patients n (%)**	**Person time (Months)**
≥1 Dose	2,356 (100)	84,023.5
≥6	2,038 (86.5)	82,431.0
≥12	1,675 (71.1)	79,156.8
≥18	1,342 (57.0)	74,194.9
≥24	1,170 (49.7)	70,589.1
≥30	1,054 (44.7)	67,451.5
≥36	961 (40.8)	64,399.9

[redacted]

Person time per indication:		
Crohn's Disease		
Duration of exposure (Months)	**Patients n (%)**	**Person time (Months)**
≥48	799 (33.9)	57,463.1
≥60	618 (26.2)	47,638.7
≥72	395 (16.8)	32,914.6
≥84	146 (6.2)	13,469.6
≥96	29 (<1.2)	3,098.3

Data available up to 19-November-2024.
Included in the analysis are the patients and their time on Vedolizumab only.
(Vedolizumab studies C13007, C13008, C13011, MLN0002SC-3030 and MLN0002SC-3031)
Exposure duration for all patients is (last dose date - first dose date + 127).

Table SIII.1.4 Duration of exposure in Pouchitis studies

Person time per indication:		
Pouchitis		
Duration of exposure (Months)	**Patients n (%)**	**Person time (Months)**
≥1 Dose	51 (100)	498
≥6	43 (84.3)	456

Data available up to 19-November-2024.
Included in the analysis are the patients and their time on Vedolizumab only.
(Vedolizumab studies Vedolizumab-4004)
Exposure duration for all patients is (last dose date - first dose date + 127).

Table SIII.2.1 Age group and gender in studies across all indications

Cumulative for all age/gender groups (person time):						
	Male (N=1,995)		**Female (N=1,872)**		**Total (N=3,867)**	
Age group (Years)	**Patients n (%)**	**Person time Patient-Years**	**Patients n (%)**	**Person time Patient-Years**	**Patients n (%)**	**Person time Patient-Years**
<18	0	0	1 (<0.1)	2.8	1 (<0.1)	2.8

[redacted]

Cumulative for all age/gender groups (person time):						
	Male (N=1,995)		**Female (N=1,872)**		**Total (N=3,867)**	
Age group (Years)	**Patients n (%)**	**Person time Patient-Years**	**Patients n (%)**	**Person time Patient-Years**	**Patients n (%)**	**Person time Patient-Years**
18 - <45	1,407 (70.5)	4,380.9	1,300 (69.4)	3719.8	2,707 (70.0)	8100.7
45 - <65	521 (26.1)	1,859.9	504 (26.9)	1786.4	1,025 (26.5)	3646.3
≥65	67 (3.4)	220.0	67 (3.6)	209.4	134 (3.5)	429.3
Total	**1,995 (100.0)**	**6,460.8**	**1,872 (100.0)**	**5,718.4**	**3,867 (100.0)**	**12,179.2**

Data available up to 19-November-2024.
Studies included: C13006, C13007, C13008, C13011, MLN0002SC-3027, MLN0002SC-3030, MLN0002SC-3031 and Vedolizumab-4004.

Table SIII.2.2 Age group and gender in ulcerative colitis studies

Person time per age/gender group:						
Ulcerative Colitis						
	Male (N=852)		**Female (N=608)**		**Total (N=1,460)**	
Age group (Years)	**Patients n (%)**	**Patient-Years**	**Patients n (%)**	**Patient-Years**	**Patients n (%)**	**Patient-Years**
<18	0	0	0	0	0	0
18 - <45	541 (63.5)	1,807.9	406 (66.8)	1,390.4	947 (64.9)	3,198.3
45 - <65	270 (31.7)	999.9	171 (28.1)	707.2	441 (30.2)	1,707.0
≥65	41 (4.8)	133.6	31 (5.1)	96.8	72 (4.9)	230.4
Total	**852 (100.0)**	**2,941.4**	**608 (100.0)**	**2,194.4**	**1,460 (100.0)**	**5,135.8**

Data available up to 19-November-2024.
Studies included: C13006, C13008, MLN0002SC-3027, and MLN0002SC-3030.

[redacted]

Table SIII.2.3 Age group and gender in Crohn's disease studies

Person time per age/gender group:						
Crohn's Disease						
	Male (N=1,111)		**Female (N=1,245)**		**Total (N=2,356)**	
Age group (Years)	**Patients n (%)**	**Patient-Years**	**Patients n (%)**	**Patient-Years**	**Patients n (%)**	**Patient-Years**
<18	0	0	1 (<0.1)	2.8	1 (<0.1)	2.8
18 - <45	848 (76.3)	2557.8	881 (70.8)	2318.7	1,729 (73.4)	4,876.5
45 - <65	238 (21.4)	849.9	327 (26.3)	1074.7	565 (24.0)	1,924.6
≥65	25 (2.3)	85.4	36 (2.9)	112.5	61 (2.6)	198.0
Total	**1,111 (100.0)**	**3,493.1**	**1,245 (100.0)**	**3508.8**	**2,356 (100.0)**	**7,002.0**

Data available up to 19-November-2024.
Studies included: C13007, C13008, C13011, MLN0002SC-3031 and MLN0002SC-3030.

Table SIII.2.4 Age group and gender in Pouchitis studies

Person time per age/gender group:						
Pouchitis						
	Male (N=32)		**Female (N=19)**		**Total (N=51)**	
Age group (Years)	**Patients n (%)**	**Patient-Years**	**Patients n (%)**	**Patient-Years**	**Patients n (%)**	**Patient-Years**
<18	0	0	0	0	0	0
18 - <45	18 (56.3)	15	13 (68.4)	11	31 (60.8)	26
45 - <65	13 (40.6)	10	6 (31.6)	5	19 (37.3)	15
≥65	1 (3.1)	1	0	0	1(2.0)	1
Total	**32 (100.0)**	**26**	**19 (100.0)**	**16**	**51 (100.0)**	**42**

Data available up to 19-November-2024.
Studies included: Vedolizumab-4004.

[redacted]

Table SIII.3.1 Dose of exposure in studies across all indications

Cumulative for all doses of exposure (person time):		
Dose of exposure	**Patients n (%)**	**Person time (Months)**
300 mg IV	3,867 (100)	114,895
108 mg SC	811 (21)	32,247
Total*	**3,867 (100)**	**146,151**

Included in the analysis are the patients and their time on Vedolizumab only.
Studies included: C13006, C13007, C13008, C13011, MLN0002SC-3027, MLN0002SC-3030, MLN0002SC-3031 and Vedolizumab-4004.
Exposure duration for all patients is (last dose date - first dose date + 127).
*All subjects in MLN0002SC-3027 and MLN0002SC-3031 received at least 1 IV dose of vedolizumab. Some patients in MLN0002SC-3027 and MLN0002SC-3031 then received an SC dose in the same study. Additionally, some MLN0002SC-3027 and MLN0002SC-3031 patients rolled over to 3030 and got SC in that study.

Table SIII.3.2 Dose of exposure in ulcerative colitis studies

Person time per dose of exposure:		
Ulcerative Colitis		
Dose of exposure	**Patients n (%)**	**Person time (Months)**
300 mg IV	1,460 (100)	48,958
108 mg SC	304 (21)	13,139
Total*	**1,460 (100)**	**61,629**

Included in the analysis are the patients and their time on Vedolizumab only.
Studies included: C13006, C13008, MLN0002SC-3027, and MLN0002SC-3030
Exposure duration for all patients is (last dose date - first dose date + 127).
*All subjects in MLN0002SC-3027 received at least 1 IV dose of vedolizumab. Some patients in MLN0002SC-3027 then received an SC dose in the same study. Additionally, some MLN0002SC-3027 patients rolled over to 3030 and got SC in that study.

Table SIII.3.3 Dose of exposure in Crohn's disease studies

Person time per dose of exposure:		
Crohn's Disease		
Dose of exposure	**Patients n (%)**	**Person time (Months)**
300 mg IV	2,356 (100)	65,440

[redacted]

Person time per dose of exposure:		
Crohn's Disease		
Dose of exposure	**Patients n (%)**	**Person time (Months)**
108 mg SC	507 (22)	19,108
Total*	**2,356 (100)**	**84,024**

Included in the analysis are the patients and their time on Vedolizumab only.
Studies included: C13007, C13008, C13011, MLN0002SC-3031, and MLN0002SC-3030.
Exposure duration for all patients is (last dose date - first dose date + 127).
* All subjects in MLN0002SC-3027 and MLN0002SC-3031 received at least 1 IV dose of vedolizumab. Some patients in MLN0002SC-3027 and MLN0002SC-3031 then received an SC dose in the same study. Additionally, some MLN0002SC-3027 and MLN0002SC-3031 patients rolled over to 3030 and got SC in that study..

Table SIII.3.4 Dose of exposure in Pouchitis studies

Person time per dose of exposure:		
Crohn's Disease		
Dose of exposure	**Patients n (%)**	**Person time (Months)**
300 mg IV	51 (100)	498
108 mg SC	0 (0)	0
Total	**51 (100)**	**498**

Included in the analysis are the patients and their time on Vedolizumab only.
Studies included: Vedolizumab-4004.
Exposure duration for all patients is (last dose date - first dose date + 127).

[redacted]

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

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

Use in Patients with Renal Impairment	
Reason for exclusion:	Patients with renal impairment were excluded to ensure standardisation of the study population.
Is it considered to be included as missing information?	No.
Rationale:	Vedolizumab does not require renal excretion and was not found to be nephrotoxic in nonclinical studies.

Use in Patients with Hepatic Impairment	
Reason for exclusion:	Patients with hepatic impairment were excluded to ensure standardisation of the study population.
Is it considered to be included as missing information?	No.
Rationale:	There is no evidence to suggest that the safety profile is expected to be different in this population. Vedolizumab does not require hepatic metabolism and there are no specific recommendations for the treatment of patients with hepatic impairment.

Use in Cardiac Impairment	
Reason for exclusion:	Patients with cardiac impairment were excluded to ensure standardisation of the study population.
Is it considered to be included as missing information?	No.
Rationale:	Nonclinical studies show no evidence of cardiotoxic effects of vedolizumab. In pivotal trials cardiac events were not more common among vedolizumab-treated patients and were related to pre-existing cardiac conditions, such as coronary artery disease.

Use in Elderly	
Reason for exclusion:	Elderly patients were excluded to ensure standardisation of the study population.

[redacted]

Use in Elderly	
Is it considered to be included as missing information?	No.
Rationale:	No evidence that the safety profile is expected to be different from that of the 18-64 years' population. There are no specific differences in the posology for vedolizumab in elderly patients as compared to those <65 years of age, and specifically, there is no requirement for dosing changes due to co-medications or decreases in renal/hepatic function that may occur with increasing age.

Use in Pregnancy and Lactation	
Reason for exclusion:	Patients were excluded due to ethical considerations.
Is it considered to be included as missing information?	Yes.
Rationale:	Not applicable.

Use in Paediatric Patients	
Reason for exclusion:	Patients were excluded due to ethical considerations.
Is it considered to be included as missing information?	No.
Rationale:	No evidence that the safety profile is expected to be different from adult population. The paediatric clinical development programme is on-going.

Patients with prior exposure to natalizumab or rituximab	
Reason for exclusion:	To assess progressive multifocal leukoencephalopathy (PML) risk with vedolizumab exposure, unconfounded by prior natalizumab or rituximab exposure.
Is it considered to be included as missing information?	No.
Rationale:	Progressive multifocal leukoencephalopathy is a potential risk. There is no additional safety concern being addressed in this population.

[redacted]

Patients with Malignancy	
Reason for exclusion:	Biologic therapies have been associated with an increased risk of cancers and patients with IBD are at increased risk of colon cancer.
Is it considered to be included as missing information?	No.
Rationale:	Included as a potential risk.

Evidence of or treatment for *Clostridium difficile* infection within 60 days or other intestinal pathogen within 30 days before enrolment	
Reason for exclusion:	To ensure that assessment of the risk of gut infection potentially associated with vedolizumab exposure was not confounded by pre-existing clostridia infections.
Is it considered to be included as missing information?	No.
Rationale:	Included as a potential risk.

Active or Latent Tuberculosis	
Reason for exclusion:	To ensure that assessment of the risk of gut infection potentially associated with vedolizumab exposure was not confounded by pre-existing tuberculosis infections.
Is it considered to be included as missing information?	No.
Rationale:	Infection including tuberculosis infection is considered a potential risk.

Mild ulcerative colitis (UC)/Crohn's disease (CD)	
Reason for exclusion:	Vedolizumab has been developed to help meet the need for treatment in patients with moderately to severely active Crohn's disease or UC that has been hard to treat successfully with conventional therapy or a monoclonal antibody (TNFα) antagonist.
Is it considered to be included as missing information?	No
Rationale:	There is no specific safety concern.

[redacted]

Chronic hepatitis B or C infection	
Reason for exclusion:	To ensure that assessment of any infection risk associated with exposure to vedolizumab was not confounded by pre-existing conditions.
Is it considered to be included as missing information?	No.
Rationale:	As vedolizumab does not cause systemic immunosuppression, treatment with vedolizumab in patients with controlled infections is not expected to be a safety risk.

Positive progressive multifocal leukoencephalopathy (PML)	
Reason for exclusion:	To ensure accurate assessment of PML risk with vedolizumab exposure.
Is it considered to be included as missing information?	No.
Rationale:	Included as a potential risk.

Patients with history of live vaccines within 30 days of treatment start, except influenza vaccine	
Reason for exclusion:	Biologics have been known to impair response to live vaccines.
Is it considered to be included as missing information?	No.
Rationale:	The results of the mechanistic studies do not suggest that live vaccinations will present a safety hazard for vedolizumab-exposed patients, but this lack of data is reflected in Section 4.4 of the SmPC, in common with other biologic agents.

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.

[redacted]

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

Table SIV.2 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant co-morbidities: Patients with hepatic impairment Patients with renal impairment Patients with cardiovascular impairment Immunocompromised	 Not included in the clinical development program. Not included in the clinical development program. Not included in the clinical development program. Not included in the clinical development program.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	Not applicable.
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Other Elderly patients (>64 yrs)	There was limited exposure in patients 65-80 years, 134 patients (3.5%) in the clinical development program. Patients >80 years were not included in the clinical development program.

[redacted]

Part II: Module SV - Post-authorisation experience

SV.1. Post-authorisation exposure

SV.1.1. Method used to calculate exposure

The methodology used to calculate the post-marketing exposure to vedolizumab is based on drug product shipping data for both vedolizumab vials (IV exposure) and pens (SC exposure). Intravenous exposure assumes that the dosage interval was once every 8 weeks and SC exposure assumes that the dosage interval was once every 2 weeks based on the current reference safety information (RSI). The total estimated exposure is an addition of IV and SC exposure. The total estimated exposure is an addition of IV and SC exposure.

SV.1.2. Exposure

Based on the above methodology, cumulative global patient exposure is estimated to be approximately 1,816,380 patient-years since launch to 31-October-2024. The estimated patient exposure for vedolizumab is presented in Table SV.1.

Table SV.1 Exposure table by Region

Region	Cumulative Patient-Years Since Launch*
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Total###	**1,816,380**

Post authorisation exposure data is included till cut off date 31-October-2024.

[redacted]

###The difference in the total and individual entries is due to rounding off.

[redacted]

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

Potential for misuse for illegal purposes

Not applicable.

[redacted]

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):

Rash, Pruritus, Eczema, Erythema, Night sweats, Acne**,** Pyrexia, Anal fissure, Nausea, Dyspepsia, Constipation, Abdominal distension, Flatulence, Haemorrhoids, Oropharyngeal pain, Nasal congestion, Cough, Arthralgia, Headache, Paraesthesia, Hypertension, Feeling cold.

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 applicable.

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 applicable.

Known risks that do not impact the risk-benefit profile

Not applicable.

Other reasons for considering the risks not important:

Not applicable.

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

Important Identified Risks	**Risk-benefit impact**
Infusion-related reactions (IRRs), including hypersensitivity reactions (HSRs).	IRRs, including HSRs, are an important identified risk based on the knowledge of the therapeutic class and the rates observed in the vedolizumab clinical development program.
Upper Respiratory Tract Infections	Upper respiratory tract infections are an important identified risk based on the knowledge of the therapeutic class and the rates observed in the vedolizumab clinical development program.

Important Potential Risks	**Risk-benefit impact**
Infections • Gastrointestinal infections and systemic infections (serious and nonserious) against which the gut constitutes a defensive barrier	Infections are an important potential risk based on the knowledge of the therapeutic class and the rates observed in the vedolizumab clinical development program. PML is known to be associated with natilizumab and was considered

[redacted]

Important Potential Risks	Risk-benefit impact
• Other serious infections, including opportunistic infections such as PML	an AE of special interest in the vedolizumab clinical development program.
Malignancy	Malignancies are an important potential risk based on the knowledge of the therapeutic class. Overall, results from the vedolizumab clinical development program to date do not suggest an increased risk for malignancy with vedolizumab treatment, however long-term data is limited.
Liver Injury	The identification of liver injury as a new safety concern was a recommendation from the Pharmacovigilance Risk Assessment Committee (PRAC) in 2016 (procedure number EMEA/H/C/PSUSA/00010186/201511) following a review of clinical and post-marketing events of liver injury. Vedolizumab does not require hepatic metabolism.

Missing Information	Risk-benefit impact
Use in Pregnancy and Lactation	Pregnant and lactating patients were excluded from the vedolizumab clinical development program. Post-marketing data does not indicate that the safety profile for pregnant and lactating patients differs from the non-pregnant/ non-lactating population.
Long-term safety	Long-term safety has been identified as missing information because limited data about the use of vedolizumab is available from the clinical development program. There is no evidence to suggest a different safety profile with long-term use.

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

Justification for the removal of safety concern

The missing information 'Long term safety' has been removed from the list of safety concerns following completion of SC formulation phase 3, long-term extension, category 3 study MLN0002SC 3030.

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

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

Not applicable.

SVII.3.2. Presentation of the missing information

Not applicable.

[redacted]

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

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

Specific adverse reaction follow-up questionnaires:

Not applicable

Other forms of routine pharmacovigilance activities

Not applicable

III.2. Additional pharmacovigilance activities

Not applicable

III.3. Summary Table of additional Pharmacovigilance activities

Not applicable

[redacted]

Part IV: Plans for post-authorisation efficacy studies

Not applicable

[redacted]

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Not applicable

V.2. Additional Risk Minimisation Measures

Not applicable

V.3. Summary of risk minimisation measures

Not applicable

[redacted]

Part VI: Summary of the risk management plan

Summary of risk management plan for Entyvio® (Vedolizumab)

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

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

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

I. The medicine and what it is used for

Entyvio is authorised for ulcerative colitis (UC), Crohn's disease (CD) and chronic pouchitis (see SmPC for the full indications). It contains vedolizumab as the active substance and it is available as powder for concentrate for solution for infusion and as solution for injection, to be administered by intravenous infusion (UC, CD and Pouchitis) or by subcutaneous injection (UC and CD only) respectively.

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

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

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

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

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

Together, these measures constitute routine risk minimisation measures.

[redacted]

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.

II.A List of important risks and missing information

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

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

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 Entyvio.

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

There are no studies required for Entyvio.

[redacted]

Part VII: Annexes

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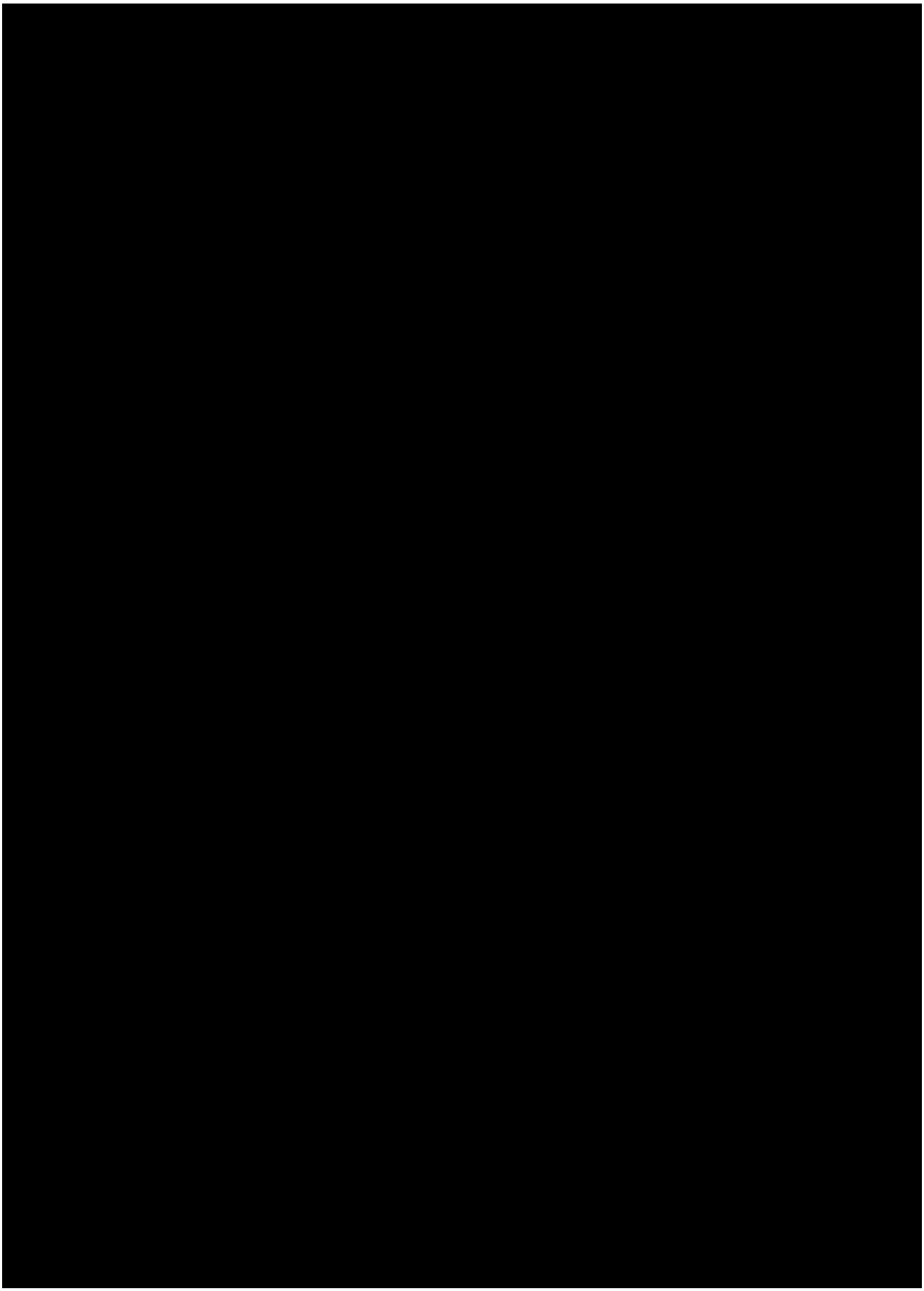


Annex 4 Specific adverse drug reaction follow-up forms

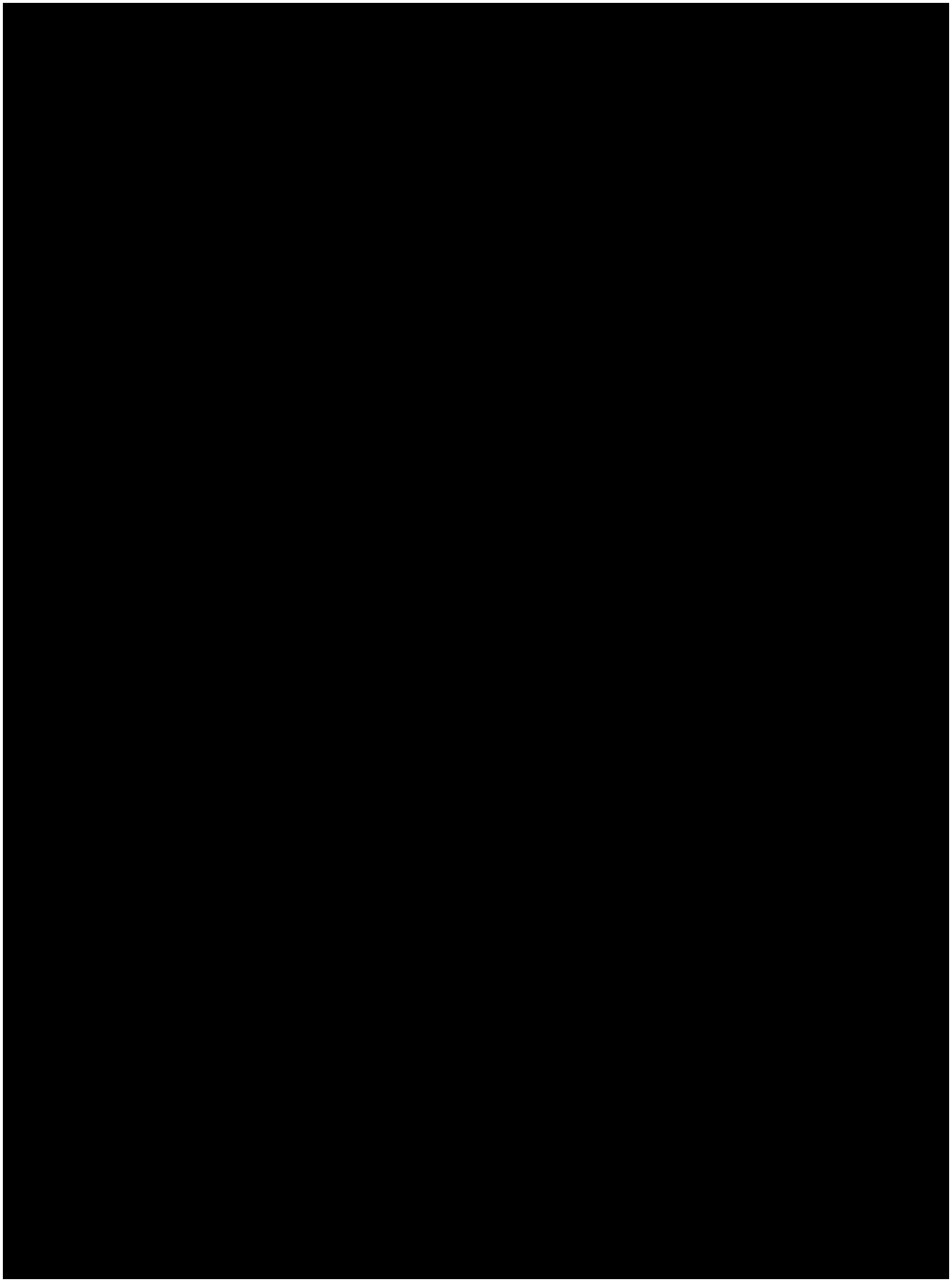
Not applicable.

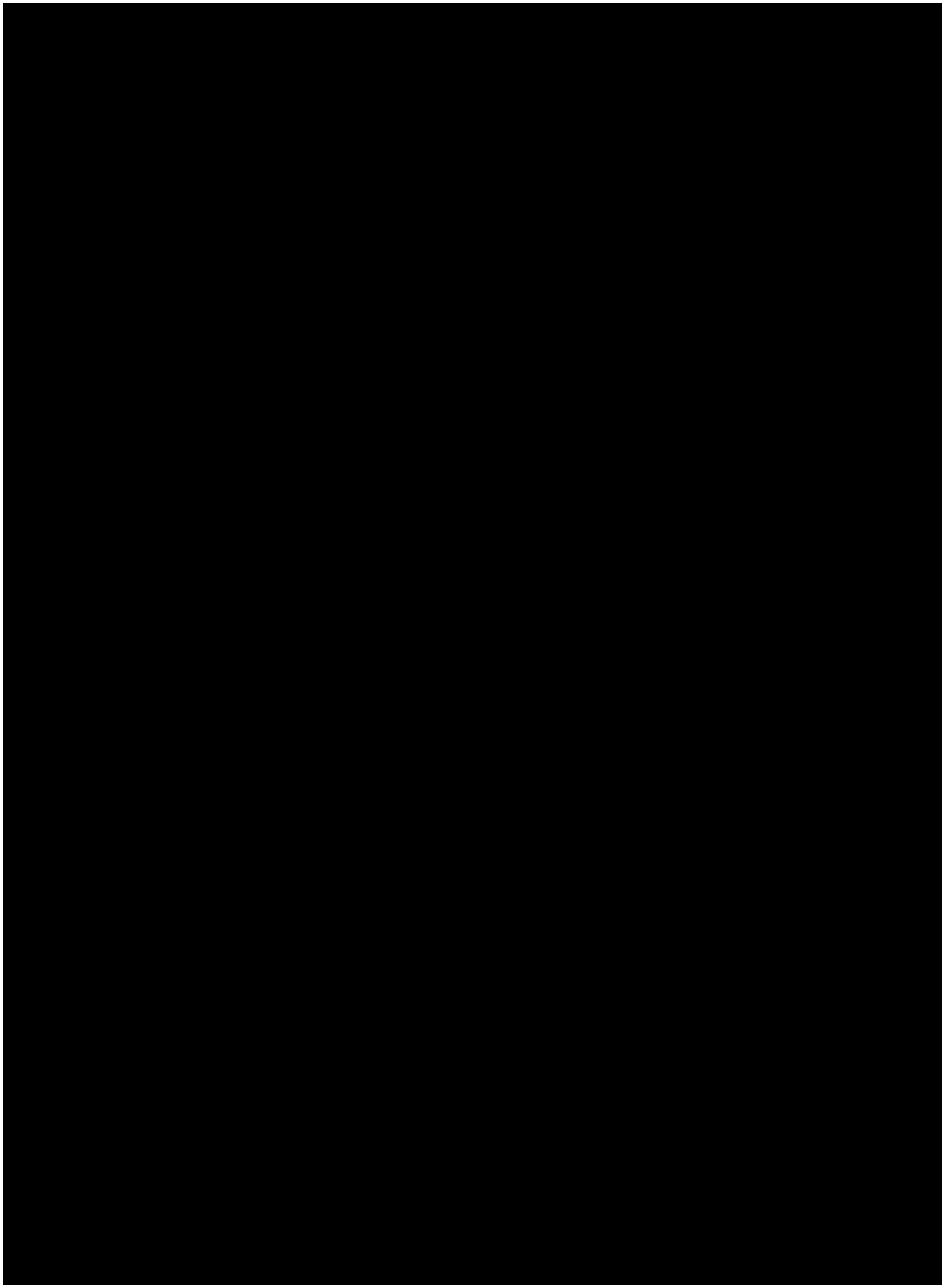
[redacted]

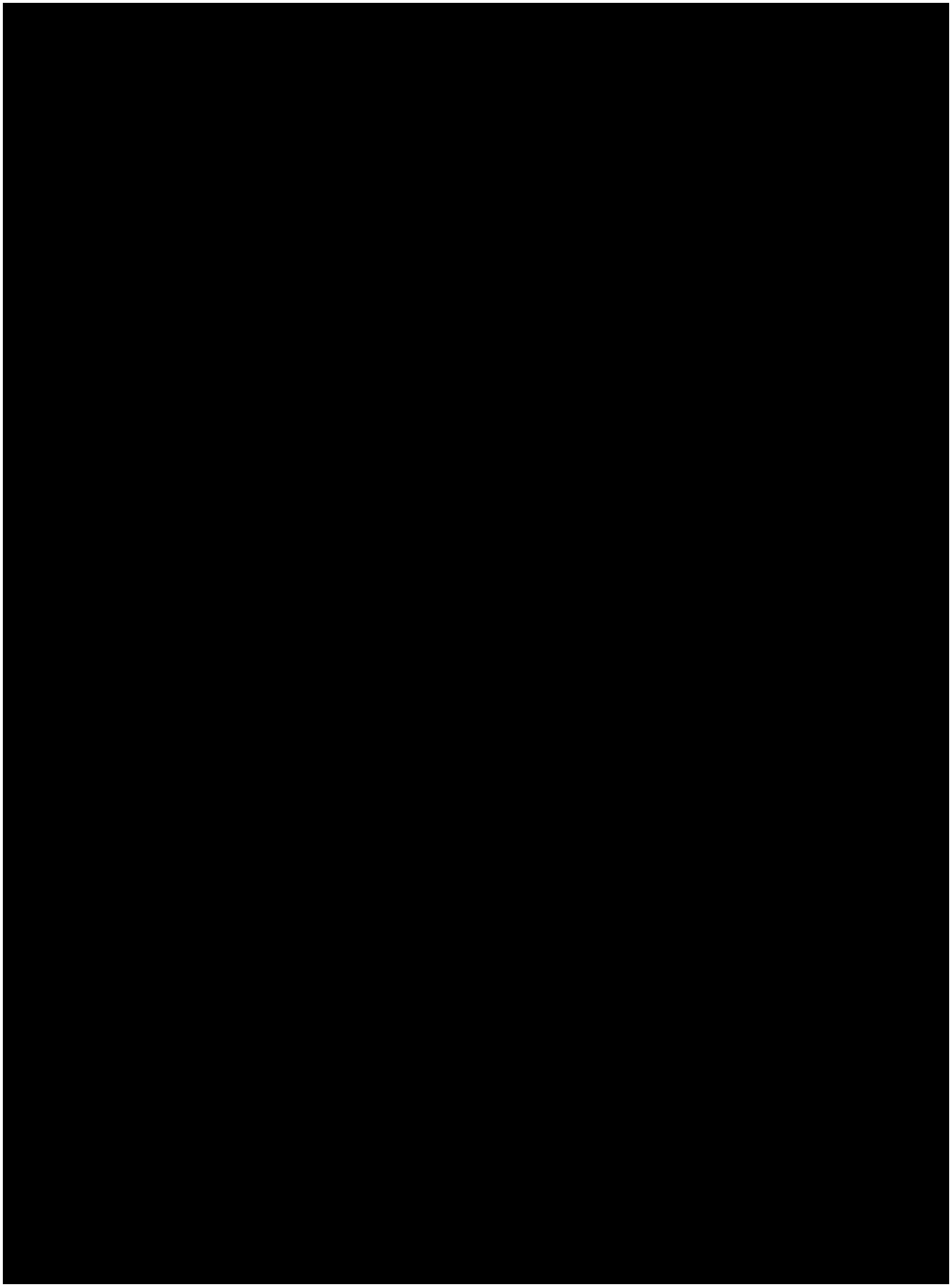
[redacted]

Annex 6 Details of proposed additional risk minimisation activities

Not applicable.







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