EU Risk Management Plan (Version 1.2)

Global Patient Safety
Signatory information is available on request.

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EU Risk Management Plan for Mirikizumab (INN or common name)

RMP version to be assessed as part of the application: 1.2

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Rationale for submitting an updated RMP: Application of Crohn's disease (CD) as a new indication, which includes data from new pivotal Phase 3 Study AMAM, Integrated IBD, and updated All Mirikizumab data, including updated tables, figures, and listings for exposures and adverse events in the All IBD Mirikizumab and All Mirikizumab Integrated Analysis Sets.

Summary of significant changes in this RMP:

Version 1.1:

- Part I updated to include UC as "current" approved indication and CD as "proposed" new indication for this RMP submission. Indication and dosage updated to align revisions in the SmPC and pharmaceutical forms and strengths updated to include text for maintenance therapy for both UC and CD.
- Module SI.2 (epidemiology section) updated to add new proposed CD indication.
- Module SIII updated to include clinical trial exposure data from CD Miri and All IBD Miri Exposures Integrated Analysis Set. Also, All Miri and UC Miri Exposures Integrated Analysis Set updated with latest available data.
- Module SV updated with the available post-marketing sales data.
- Module SVII.3 updated with safety data from the CD development programme. The characterisation of each risk was updated to include the CD placebo-controlled induction data, All IBD, and All Miri data.
- Most recent naming for the follow-up forms updated throughout the document.
- Study aliases and CD population added into the proposed additional pharmacovigilance activities for Studies I6T-MC-B003 and I6T-MC-B004.

Version 1.2:

- Modules SIII and SVII.3.1 were updated with data for exposures and adverse events in the All IBD Mirikizumab and All Mirikizumab Integrated Analysis Sets.

Other RMP versions under evaluation

RMP version number: None

Submitted on: Not applicable

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Details of the currently approved RMP

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

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List of Abbreviations

Term	Definition
AE	adverse event
ADR	adverse drug reaction
AIH	autoimmune hepatitis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASA	amino salicylic acid
AST	aspartate aminotransferase
CCV	cerebrocardiovascular
CD	Crohn's disease
CHD	coronary heart disease
CI	confidence interval
COVID-19	coronavirus disease 2019
CRC	colorectal cancer
DILI	drug-induced liver injury
DVT	deep venous thrombosis
EAIR	exposure-adjusted incidence rate
EIMs	extraintestinal manifestations
ePPND	enhanced pre- and post-natal development
GGT	gamma-glutamyl transpeptidase
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	hazard ratio
ICH	International Council for Harmonisation
IBD	inflammatory bowel disease
IgG	immunoglobulin
IL	interleukin
IR	incidence rate
IRR	incidence rate ratio
IV	intravenous
MACE	major adverse cardiac event
MI	myocardial infarction
Miri	mirikizumab
NAFLD	non-alcoholic fatty liver disease
NMSC	non-melanoma skin cancer
NOAEL	no-observed-adverse-effect level
OR	odds ratio

Term	Definition
PE	pulmonary embolism
PIL	Patient Information Leaflet
PSC	primary sclerosing cholangitis
PY	person years
PYE	patient-years of exposure
Q8W	every 8 weeks
RMP	risk management plan
RR	relative risk
SAE	serious adverse event
SC	subcutaneous
SmPC	summary of product characteristics
SIR	standardised incidence ratio
SMR	standardised mortality ratio
TEAE	treatment-emergent adverse event
TB	tuberculosis
TNF	tumour necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
VTE	venous thromboembolism

Part I: Product(s) Overview

Table Part I.1. Product Overview

Active substance(s) (INN or common name)	Mirikizumab (LY3074828)
Pharmacotherapeutic group(s) (ATC Code)	L04AC24
Marketing authorisation holder	Eli Lilly and Company
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	Omvoh
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Humanised IgG4 variant monoclonal antibody
	Summary of mode of action: Mirikizumab is a humanised IgG4–variant monoclonal antibody that binds to the p19 subunit of IL-23
	Important information about its composition: Mirikizumab is a gene recombinant product, and the cell line used to produce mirikizumab was derived from host cell line CHO, which was derived from an adult CHO.
Hyperlink to the Product Information	The current PI is included in eCTD sequence 1.3.1.
Indication(s) in the EEA	**Current:** Adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment.
	Proposed: Adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment.
Dosage in the EEA	**Current:** For UC, the recommended mirikizumab dose regimen has 2 parts: 1. Induction dose: The induction dose is 300 mg by intravenous infusion (i.v.) for at least 30 minutes at Weeks 0, 4, and 8. 2. Maintenance dose: The maintenance dose is 200 mg (i.e. 2 pre-filled syringes or 2 pre-filled pens) by subcutaneous injection every 4 weeks, after the completion of induction dosing.
	Proposed: For CD, the recommended mirikizumab dose regimen has 2 parts: 1. Induction dose: The induction dose is 900 mg (3 vials with 300 mg each) by intravenous infusion (i.v.) for at least 90 min at Weeks 0, 4, and 8. 2. Maintenance dose: The maintenance dose is 300 mg (i.e. 1 pre-filled syringe or pen with 100 mg/1 mL and 1 pre-filled syringe or pen with 200 mg/2 mL) by subcutaneous injection every 4 weeks, after the completion of induction dosing. The 1-mL and 2-mL injections may be administered in any order.

	The 2-mL pre-filled syringe and 2-mL pre-filled pen are only for treatment of CD.
Pharmaceutical form(s) and strengths	**Current:** Infusion: The medicinal drug product mirikizumab for IV infusion for the induction treatment of UC is supplied as a single-use concentrate solution for infusion in a glass vial and is composed of mirikizumab and the inactive ingredients sodium citrate dihydrate, citric acid anhydrous, sodium chloride, polysorbate 80, and water for injection. Pharmaceutical strength is 300 mg/15 mL (20 mg/mL). SC injection: The currently marketed medicinal drug product mirikizumab for the maintenance treatment of UC is supplied as 100 mg/mL solution in a 1-mL pre-filled syringe or pre-filled pen and is composed of mirikizumab and the inactive ingredients sodium citrate dihydrate, citric acid anhydrous, sodium chloride, polysorbate 80, and water for injection. Pharmaceutical strength is 100 mg/mL.
	Proposed: Infusion: The formulation of the single-use concentrate solution for infusion in a glass vial remains unchanged. SC injection: For the maintenance treatment of UC a revised 100-mg/mL solution in a 1-mL pre-filled syringe or pre-filled pen is supplied and is composed of mirikizumab and the inactive ingredients L-histidine, L-histidine hydrochloride monohydrate, sodium chloride, mannitol, polysorbate 80, and water for injection. For the maintenance treatment of CD, the revised citrate-free 100 mg/1 mL solution in a 1-mL pre-filled syringe or pre-filled pen is supplied, as well as an additional medicinal drug product of 200 mg/2 mL in a pre-filled syringe or pre-filled pen. This 200 mg/2 mL solution is composed of mirikizumab and the inactive ingredients L-histidine, L-histidine hydrochloride monohydrate, sodium chloride, mannitol, polysorbate 80, and water for injection.
Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: ATC = anatomical therapeutic chemical; CHO = Chinese hamster ovary; CD = Crohn's disease; eCTD = electronic common technical document; EEA = European Economic Area; IgG = immunoglobulin G; IL = interleukin; INN = International Non-Proprietary Name; IV = intravenous; PI = package insert; RMP = risk management plan; SC = subcutaneous; UC = ulcerative colitis.

Part II: Safety Specification

Module SI - Epidemiology of the Indication(s) and Target Population(s)

SI.1 Ulcerative Colitis

SI.1.1 Incidence

The incidence of UC worldwide varies by country and/or geographical location and has been increasing over time (Benchimol et al. 2011; Benchimol et al. 2014; Ungaro et al. 2017). Geographically, the highest IRs of UC have been found in northern Europe while the lowest IRs have been reported in Asia and the South America (Ng et al. 2017).

In the US, from 2000 through 2010, the adjusted annual IR of UC was 12.2 per 100 000 PY and it was higher among males (14 cases per 100 000 PY) compared to females (10.7 per 100 000 PY) (Shivashankar et al. 2017).

The IRs of UC in Europe vary by country. In the UK, reported IRs of UC range from 14.3 to 23.2 per 100 000 PY (Hamilton et al. 2020; King et al. 2020; Pasvol et al. 2020) and the incidence of UC in the UK was found to be higher among males (24.2 per 100 000 PY) compared to females (22.1 per 100 000 PY). The incidence of UC was found to be 18.6 per 100 000 PY in 2013 in Denmark (Lophaven et al. 2017), 20.6 per 100 000 PY in 2017 in Norway (Lirhus et al. 2021), and 8.1 per 100 000 PY in 2017 in Spain (Chaparro et al. 2021).

In Asia and the Middle East, the reported annual IRs of UC range from 0.1 to 6.3 per 100 000 PY (Ng et al. 2014; Ananthakrishnan et al. 2015; Ungaro et al. 2017).

SI.1.2 Prevalence

Similar to the incidence, the prevalence of UC varies by country and or geographical location (Molodecky et al. 2012; Ananthakrishnan et al. 2015). Geographically, the highest prevalence of UC has been reported in Europe while the lowest has been reported in Asian regions (Ng et al. 2017).

In the US, the point prevalence of UC in 2011 was 286.3 cases per 100 000 persons (Shivashankar et al. 2017); it was highest in Whites (89 per 100 000 persons), lowest in Blacks (25 per 100 000 persons), 35 per 100 000 persons among Hispanics, and 40 per 100 000 persons among Asian Americans (Wang et al. 2013). In Europe, the prevalence of UC varies by country. The prevalence of UC was 412/100 000 in an insurance-based cohort study in Germany (Hein et al. 2014), 570/100 000 population in 2017 in the UK (King et al. 2020) and 88.7/100 000 in Spain (Marín-Jiménez et al. 2018).

Although the lowest prevalence of UC has been found in Asian regions, multiple studies have reported increasing prevalence of UC in Asian countries over time. In Hong Kong, the prevalence of UC increased from 2.3 to 6.99 per 100 000 over a 9-year period (Lok et al. 2008). In Japan the prevalence of UC increased from 7.85 to 63.6 per 100 000 persons between 1984 and 2005 (Higashi et al. 1988; Asakura et al. 2009), whereas in South Korea, the prevalence of

UC increased from 0.34 to 76.66 per 100 000 between 1986 and 2015 (Yang et al. 2008; Park et al. 2019).

SI.1.3 Demographics of the Population in the authorised Indication – (age, gender, racial, and/or ethnic origin) and Risk Factors for the Disease

Age

Generally, the incidence of UC increases gradually from childhood through young adulthood with mean age onset between 20 and 40 years (Lophaven et al. 2017; Shivashankar et al. 2017). Although some studies have found that the incidence (Keyashian et al. 2019) and prevalence (Kappelman et al. 2013) of UC increases with advancing age, most studies have found that the association between UC and age shows a bimodal pattern with peaks in both young adults and elderly age groups (Shapiro et al. 2016; Lophaven et al. 2017; King et al. 2020).

Gender

Associations between gender and the risk for UC vary by country and or study. In the US and UK some studies have found females to have a significantly lower risk for UC compared to males (Shivashankar et al. 2017; King et al. 2020). However, a population-based retrospective cohort study in a western Canadian province found no significant difference in the risk for UC between males and females (Osei et al. 2020). In a nationwide population-based cohort study in Denmark, the incidence of UC was higher among females compared to males (Lophaven et al. 2017), whereas in a nationally representative annual survey of the civilian non-institutionalised population in the US, the risk of UC was significantly higher among females compared to males (OR = 1.81, 95% CI = 1.20-2.72) (Wang et al. 2013).

Race and ethnicity

In terms of race, in a nationally representative annual survey of the non-institutionalised civilian population in the US conducted between 1996 and 2007, the majority (77%) of adult UC patients were found to be White and the prevalence of UC was found to be significantly less among Blacks compared to Whites (OR = 0.27; 95% CI = 0.10-0.74) (Wang et al. 2013). Similarly, in an electronic health record-based cohort study in the US, both Black adults (OR = 0.41; 95% CI = 0.40-0.43) and Hispanic adults (OR = 0.45; 95% CI = 0.44-0.46) were found to be significantly less likely to be diagnosed with UC than White adults (Barnes et al. 2021).

Risk factors

Although the causes of IBD including UC are poorly understood, family history is one of the strongest established risk factors. Moreover, 8% to 14% of patients with UC have a family history of IBD with first-degree relatives having 4 times the risk of developing UC (Ungaro et al. 2017). Genetic risk factors have also been identified in over 200 genetic loci via genome-wide association studies (Ungaro et al. 2017). The rising incidence of UC is suggestive of environmental risk factors with former smoking established as a major risk factor associated with UC (OR = 1.79; 95% CI = 1.37-2.34) (Ungaro et al. 2017).

SI.1.4 Main Existing Treatment Options

Commonly used medications for induction of remission of UC include 5-ASA, corticosteroids, biologic therapies such as adalimumab, infliximab, golimumab and vedolizumab, small molecule Janus kinase inhibitors including tofacitinib, and sphingosine-1 receptor modulators including ozanimod. Once remission is induced, the same medications except corticosteroids can be used to maintain remission, often at a lower dose. An administrative claims study of 516 UC patients in Taiwan demonstrated the following medication use in the 90 days preceding first UC diagnosis: 5-ASA (25.19%), azathioprine (0.19%), and steroids (16.67%) (Keller et al. 2014). In Denmark, a national, clinically based cohort of 267 previously naive TNF-inhibitor-treated UC patients reported the following medication use: 5-ASA (38.20%), glucocorticoids (49.10%), azathioprine (19.48%), and methotrexate (0.75%) (Bank et al. 2015). In the US, biologic use rates increased significantly from 2007 to 2016, from 131 per 1000 PY in 2007 (95% CI = 121-140) to 589 per 1000 PY in 2016 (95% CI = 575-604; p<.001) (Barnes et al. 2020).

SI.1.5 Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity

Ulcerative colitis is a chronic relapsing and remitting disease characterised by inflammation, ulceration, and bleeding in the colon (Sifuentes-Dominguez et al. 2016). Up to 15% of patients may present with severe disease (Ungaro et al. 2017). Symptoms at presentation may include urgency to defecate, faecal incontinence, fatigue, increased frequency of bowel movements, bloody stools, nocturnal defecations, and abdominal discomfort. The clinical presentation varies based on the extent of colonic involvement. Patients with proctitis may present predominantly with urgency and tenesmus, whereas in pancolitis, bloody diarrhoea and abdominal pain may be more frequent (Ungaro et al. 2017).

Although the pathogenesis of UC shows similarities in patients affected in childhood and adulthood, paediatric patients with UC have demonstrated more extensive disease and more severe disease course compared with adult patients with UC (Jakobsen et al. 2011). Clinical presentation depends on the site and extent of mucosal inflammation, with the most common symptoms in paediatric patients with UC being weight loss, rectal bleeding, diarrhoea, urgency to defecate, and abdominal pain (Diefenbach et al. 2006).

Overall risk of EIMs ranges from 7% to 17% (Fumery et al. 2018), although one-third of UC patients may experience EIMs (Ungaro et al. 2017). Articular manifestations are the most frequently observed EIMs and include peripheral arthritis (5.5%) and ankylosing spondylitis (1%). Specific to spondyloarthropathy, the cumulative incidences over 10, 20, and 30 years after UC diagnoses were 5%, 14%, and 22%, respectively. Cutaneous EIMs (1.3%), PSC (0.6%) and ocular manifestations (0.6%) have also been observed in UC patients (Fumery et al. 2018).

Anaemia is a frequent complication among UC patients, with approximately 20% to 24% of UC patients anaemic at diagnosis, including 8% with severe anaemia (<10 g/dL). The frequency of anaemia appears to decrease over time, however, with only 7% of UC patients experiencing anaemia after 10 years of follow-up (Fumery et al. 2018).

Mortality

There is no clear association between UC and the overall mortality risk. Studies in certain countries have found UC to be associated with increased all-cause mortality risk. In Canada, the risk of mortality from all causes was significantly higher among UC patients compared to the general population (SMR = 1.21, 95% CI = 1.12-1.32) (Bitton et al. 2016). Additionally, in a meta-analysis of studies from various countries on IBD and the risk for mortality, the SMRs for all-cause mortality in patients with UC ranged from 0.44 to 7.14 and the all-cause mortality summary SMR for UC was found to be significantly higher than the control population (SMR = 1.16, 95% CI = 1.04-1.29); however, there was significant heterogeneity among the studies (Bewtra et al. 2013).

Several studies in other countries have found no significant association between UC and the risk of mortality from all causes when compared to either non-IBD controls or general population. There was no significant difference in the risk for all-cause mortality among UC patients in Norway (HR = 1.14, 95% CI = 0.93-1.40) (Hovde et al. 2016), Finland (SMR = 0.90, 95% CI = 0.77-1.06) (Manninen et al. 2012) and Australia (SMR = 0.82, 95% CI = 0.68–0.986) (Selinger et al. 2013).

Ulcerative colitis has also been associated with various cause specific mortality risks including significantly increased SMRs for gastrointestinal causes (2.81, 2.32-3.34), pulmonary diseases (1.24, 1.02-1.46), cardiovascular diseases (1.14, 1.06-1.22), and cancers of the colon (1.90, 1.38-2.55), rectum (1.79, 1.14-2.69) and biliary tract (5.65, 3.54-8.54) (Jussila et al. 2014).

SI.1.6 Important Comorbidities

UC has been associated with various comorbidities. Important comorbidities that are associated with UC are summarised in Table S1.1.

Table SI.1. Important Comorbidities among Patients with UC

Comorbidity	UC IR per 100 PY (or % as Indicated)	Effect Measures (95% Confidence Interval)
Cardio- and Cerebrovascular Disorders		
Major adverse cardiovascular events (MACE)	1.10 (Kristensen et al. 2013)	RR=1.17 (1.09-1.26) (Kristensen et al. 2013)
Stroke	0.22-0.45 (Choi et al. 2019b; Kristensen et al. 2014; Kristensen et al. 2013; Huang et al. 2014)	HR=1.05 (0.95-1.16) (Choi et al. 2019b) IRR=1.10 (0.99-1.22) (Kristensen et al. 2014) HR=2.05 (1.37-3.04) (Keller et al. 2014) RR=1.10 (1.02-1.19) (Kristensen et al. 2013)
Myocardial infarction	0.20-0.73 (Choi et al. 2019b; Aniwan et al. 2018; Kristensen et al. 2013)	HR=1.11 (0.99-1.24) (Choi et al. 2019b) HR=2.70 (1.69-4.35) (Aniwan et al. 2018) RR=1.17 (1.03-1.33) (Kristensen et al. 2013)
Thromboembolism		
Venous thrombo-embolism (VTE)	0.11-0.24 (Kappelman et al. 2011; Isene et al. 2014; Vegh et al. 2014)	HR=1.9 (1.8-2.0) (Kappelman et al. 2011) RR=1.64 (1.62-1.66) (Saleh et al. 2011) HR=1.27 (1.10-1.45) (Galloway et al. 2020)

Comorbidity	UC IR per 100 PY (or % as Indicated)	Effect Measures (95% Confidence Interval)
Deep venous thrombosis (DVT)	0.14-0.30 (Kappelman et al. 2011; Bernstein et al. 2001a; Liu et al. 2021)	HR=1.8 (1.6-2.0) (Kappelman et al. 2011) IRR=2.77 (2.07-3.69) (Bernstein et al. (2001a) RR=1.77 (1.74-1.80) (Saleh et al. 2011)
Pulmonary embolism (PE)	0.05-0.10 (Kappelman et al. 2011; Saleh et al. 2011; Liu et al. 2021)	HR=2.0 (1.8-2.2) (Kappelman et al. 2011) RR=1.40 (1.37-1.44) (Saleh et al. 2011)
Psychiatric disorders		
Depression	0.34-3.12 (Ludvigsson et al. 2021; Choi et al. 2019a; Bernstein et al. 2019)	HR= 1.4 (1.3-1.4) (Ludvigsson et al. 2021), HR=1.93 (1.70-2.18) (Choi et al. 2019a) IRR=1.43 (1.24-1.64) (Bernstein et al. 2019)
Suicide	0.2 (Ludvigsson et al. 2021)	HR=1.0 (0.8-1.2) (Ludvigsson et al. 2021) OR=1.9 (1.4-2.4) (Gradus et al. 2010) HR=1.26 (1.08-1.49) (Jess et al. 2013) HR=0.94 (0.42-2.12) (Bernstein et al. 2015)
Suicide attempts	0.8 (Ludvigsson et al. 2021)	HR=1.2 (1.2-1.2) (Ludvigsson et al. 2021)
Anxiety	0.38-3.12 (Ludvigsson et al. 2021; Choi et al. 2019a)	IRR=1.27 (1.11-1.44) (Bernstein et al. 2019) HR=1.58 (1.43-1.74) (Choi et al 2019a)
Bipolar disorder	0.04 (Ludvigsson et al. 2021)	IRR, 1.82 (1.33-2.50) (Bernstein et al. 2019) HR=1.2 (1.1-1.4) (Ludvigsson et al. 2021)
Malignancy		
Overall	0.33-1.34 (Burisch et al. 2022; Bernstein et al. 2001b; Biancone et al. 2016; Jess et al. 2013; Jussila et al. 2013; Taborelli et al. 2020; Jung et al. 2017; So et al. 2017; van den Heuvel et al. 2016; Karlén et al. 1999)	RR=1.18 (1.06-1.31) (Burisch et al. 2021) SIR=1.08 (1.02-1.14) (Jussila et al. 2013) SIR=1.89 (1.56-2.26) (Jung et al. 2017)
Colorectal cancer	0.07-0.25 (Jess et al. 2013; Cheddani et al. 2016)	HR=1.40 (1.23-1.59) (King et al. 2020) IRR=1.6 (1.3-2.0) (Herrinton et al. 2012) HR=1.30 (1.17-1.45) (Olén et al. 2020) HR=1.87 (1.75-2.00) (Olén et al. 2020) HR=1.66 (1.57-1.76) (Olén et al. 2020)
Lymphoma	0.04 (Bernstein et al. 2001b	IRR=1.03 (0.47-2.24) (Bernstein et al. 2001b)
Hepatic disorders		
NAFLD	Prevalence 1.5-55% (Gizard et al. 2014)	OR=2.37 (2.17-2.60) (Onwuzo et al. 2023)
PSC	0.08 (Burisch et al. 2019)	IRR=6.85 (4.27-10.97) (Burisch et al. 2019)
AIH	0.31% (Halling et al. 2017)	OR=8.6 (5.4-13.6) (Halling et al. 2017) OR=10.50 (9.55-11.55) (Tunio et al. 2021)
Cholelithiasis	0.50-0.75 (Chen et al. 2018; Parente et al. 2007) Prevalence=4.6-36.4% (Gizard et al. 2014)	OR=1.57 (1.37-1.81) (Voss et al. 2021)

Comorbidity	UC IR per 100 PY (or % as Indicated)	Effect Measures (95% Confidence Interval)
Elevated liver enzymes	19.9% (Cappello et al. 2014)	AST ≥2×ULN OR=1.86 (1.21-2.87) (Voss et al. 2021) GGT ≥2×ULN OR=1.47 (1.30-1.66) (Voss et al. 2021) GGT ≥5×ULN OR=1.89 (1.21-2.94) (Voss et al. 2021) ALP ≥2×ULN OR=4.22 (2.81-6.36) (Voss et al. 2021)
Other Autoimmune Disorders		
Rheumatoid arthritis	0.1 (Burisch et al. 2019)	IRR=1.67 (1.21-2.30) (Burisch et al. 2019) OR=1.6 (1.3-1.9) (Halling et al. 2017)
Ankylosing spondylitis	0.03 (Burisch et al. 2019)	IRR=2.76 (1.50-5.10) (Burisch et al. 2019) OR=3.9 (3.1-4.9) (Halling et al. 2017)
Celiac disease	0.04 (Burisch et al. 2019)	IRR=2.97 (1.69-5.25) (Burisch et al. 2019) OR=4.5 (3.3-6.1) (Halling et al. 2017)

Abbreviations: AIH = autoimmune hepatitis; ALP = alkaline phosphatase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transpeptidase; HR = hazard ratio; IR = incidence rate; IRR = incidence rate ratio; NAFLD = non-alcoholic fatty liver disease; OR = odds ratio; PSC = primary sclerosing cholangitis; PY = patient-years; RR = relative risk; SIR = standardised incidence rate; UC = ulcerative colitis; ULN = upper limit of normal.

SI.2 Crohn's Disease

SI.2.1 Incidence

The incidence of CD varies by country and geographic location (Ng et al. 2017). In Europe, the reported IRs for CD range from 0.4 per 100 000 PY in Moldova to 22.8 per 100 000 PY in the Netherlands (Zhao et al. 2021). The incidence of CD was estimated at 14.3 per 100 000 PY in the UK (King et al. 2020), 9.1 per 100 000 PY in 2013 in Denmark (Lophaven et al. 2017), 13.9 per 100 000 PY in 2017 in Norway (Lirhus et al. 2021), and 7.5 per 100 000 PY in Spain (Chaparro et al. 2021). In Asia, the crude IR for CD has been estimated at 0.54 per 100 000 PY (Ng et al. 2013). In the US, the incidence of CD has been estimated at 6.3 per 100 000 PY (Lewis et al. 2023).

SI.2.2 Prevalence

The prevalence of CD also varies by country and geographic location. In the US, the age-, sex-, and insurance-standardised prevalence of CD has been estimated at 305 per 100 000 population (Lewis et al. 2023). In Europe, estimates of the prevalence of CD vary widely by country ranging from 1.51 per 100 000 population in Romania (Ng et al. 2017) to 403 per 100 000 population in the UK (King et al. 2020). Worldwide, the lowest prevalence estimates for CD have been reported in Asia (1.05 per 100 000 population in Taiwan) and South America (0.9 per 100 000 population in Brazil) (Ng et al. 2017).

SI.2.3 Demographics of the Population in the proposed Indication – (Age, Gender, Racial and/or Ethnic Origin) and Risk Factors for the Disease

Age

The incidence of CD gradually increases from childhood, peaking around the third decade of life, and then gradually decreases thereafter. The prevalence of CD gradually increases from childhood and then gradually decreases after age 80 years (Lewis et al. 2023).

Gender

Associations between CD and gender vary among countries and with age. In the US, results from one study showed that among children, both the IR and the prevalence of CD were higher among males compared to females. However, among adults aged 20 years and older, both the IR and prevalence of CD were higher among females compared to males (Lewis et al. 2023). Similarly, in the UK and Denmark, among adults aged 18 years and older, both the IR and the prevalence of CD were found to be higher among females compared to males (King et al. 2020, Lophaven et al. 2017). However, in Asia, 1 study found there were more male than female patients with CD (61.4% vs 38.6%) (Ng et al. 2013).

Race and ethnicity

Data from the US indicate that the prevalence of CD is highest in Whites (154 per 100 000 population) and lowest in Hispanics (15 per 100 000 population), while the prevalence among Blacks and Asians was 68 per 100 000 population and 45 per 100 000 population, respectively (Wang et al. 2013).

Aetiology and risk factors

The exact aetiology of CD remains unknown. However, the development of IBD, including CD, possibly involves a complex interplay between genetic predisposition and the environment. Some authors have suggested CD may be due to abnormal immune response to environmental triggers among susceptible individuals (Boyapati et al. 2015). Evidence from twin, familial clustering, and genome-wide association studies indicate a possible association between CD and genetic predisposition. In large European twin studies, the concordance rate for CD in monozygotic twins was estimated at between 20% and 50%, whereas the concordance rate in dizygotic twins brought up in the same environment is less than 10% (Halme et al. 2006). The rate at which patients with CD report a family history of CD varies from 2% to 14% (Halme et al. 2006), while several genome-wide association studies have identified several single nucleotide polymorphisms at various loci that have been associated with the risk for CD (Liu et al. 2014). Environmental risk factors for CD include smoking, low fibre diet, lack of exercise, breastfeeding, and use of certain drugs, including oral contraceptives and antibiotics (Chen et al. 2019).

SI.2.4 Main Existing Treatment Options

As CD is a lifelong disease, the overall goal in the treatment and management of CD is to induce remission and achieve mucosal healing with response maintained in the long term. It is recognised that early intervention and continued monitoring may prevent complications (Torres et al. 2020). There is emerging evidence that achieving both clinical and endoscopic remission in patients with moderate-to-severe CD results in a decreased risk of disease progression (Ungaro et al. 2020).

Existing treatment options for CD include

- conventional therapies such as corticosteroids (for example, prednisone, budesonide) and immunomodulators (for example, azathioprine, 6-mercaptopurine, and methotrexate)
- biologic therapies (for example, TNFα blockers, IL-12/23 and IL-23 inhibitors, integrin receptor antagonists)
- targeted oral therapies (for example, Janus kinase inhibitor), and
- surgery, for patients who fail available therapies or develop complications beyond the scope of medical management.

Limitations of conventional therapy

Corticosteroids are used as first-line therapy but may not achieve mucosal healing. Their use is aimed at the acute control of symptoms. Corticosteroids are not recommended for long-term use given the known toxicities associated with chronic steroid exposure (Lichtenstein et al. 2018).

Thiopurines (azathioprine and 6-mercaptopurine) may be used for the maintenance of remission and are not recommended for induction therapy due to slow onset of full therapeutic effect. They have increased risk of certain malignancies, immune suppression, pancreatitis, and hepatotoxicity (Lichtenstein et al. 2018).

Methotrexate use may be considered for the maintenance of remission in patients with steroid-dependent CD or in combination with targeted therapy. Its role in induction treatment for CD is limited (Torres et al. 2020). Methotrexate has increased risk of nausea and vomiting, hepatotoxicity, pulmonary toxicity, and myelosuppression (Lichtenstein et al. 2018).

Limitations of current biologic and targeted oral treatments

Multiple studies have shown patients becoming unresponsive to, failing to tolerate, or losing response to biologic and oral targeted therapies for CD:

- approximately one-third of patients with CD treated with anti-TNFs are primary non-responders, and approximately one-third are secondary non-responders, meaning they lose response or develop intolerance after an initial benefit (Lichtenstein et al. 2018)
- discontinuation rates of up to 25% in the first 3 months of treatment, and as high as 65% at 12 months, have been reported in the US for biologic treatments (Khan et al. 2019), and
- published data, including from recently approved therapies for CD, report a lower rate of efficacy for patients who previously experienced inadequate response, loss of response, or

intolerance to biologic and advanced oral therapy (Sands et al. 2014; Derikx et al. 2023; Rinvoq package insert, 2023; Skyrizi package insert, 2024).

These limitations underscore the need for additional therapeutic options, such as mirikizumab, to provide benefit to patients with CD.

SI.2.5 Natural History of the Indicated Condition in the Population, including Mortality and Morbidity

CD is an idiopathic chronic granulomatous IBD that most commonly affects the terminal ileum and colon but can affect any part of the gastrointestinal tract as well as extraintestinal sites (Flynn et al. 2019). CD can occur at any age from childhood throughout adulthood, but it is most commonly diagnosed between 20 to 29 years of age (Shivashankar et al. 2017). Symptoms include diarrhoea, abdominal pain, and weight loss, but in some cases, suspected appendicitis may lead to the initial detection of CD while in other cases, extra-intestinal findings may be present without significant abdominal symptoms (Freeman 2014). Disease progression follows a relapsing remitting course that can lead to development of complications such as gastrointestinal strictures, fistulas, perforation, and abscess which may require surgical intervention (Flynn et al. 2019). CD can also lead to the development of extraintestinal manifestations, including dermatologic manifestations such as erythema nodosum and pyoderma gangrenosum, musculoskeletal manifestations such as peripheral arthritis and spondylitis, as well as renal manifestations such as nephrolithiasis (Levine et al. 2011; Flynn et al. 2019). In addition, patients with CD may develop various comorbidities during the course of the disease (see Section SI.2.6).

Several studies have found CD to be associated with an increased risk of all-cause mortality after adjustment for potential confounders HR=1.28 (95% CI=1.15 to 1.43) and HR=1.61 (95% CI=1.16 to 2.22) (Li et al. 2023; Follin-Arbelet et al. 2023). Some of the risk factors for mortality among patients with CD include male sex (HR=1.65, 95% CI=1.04 to 2.62), onset after 40 years of age (HR=1.72, 1.19 to 2.48), colonic disease (HR=1.57, 1.05 to 2.35), and penetrating behaviour (HR=3.3, 1.41 to 7.76) (Follin-Arbelet et al. 2023).

SI.2.6 Important Comorbidities

CD has been found to be associated with various comorbidities. The important comorbidities that have been associated with CD are summarised in Table S1.2.

Table SI.2. Important Comorbidities among Patients with CD

Comorbidity	**CD IR per 100 PY (or % as Indicated)**	**Effect Measures (95% Confidence Interval)**
Cardio- and Cerebrovascular Disorders		
Major adverse cardiovascular events (MACE)	0.82 (Kristensen et al. 2013)	RR=1.48 (1.28-1.70) (Kristensen et al. 2013)
Stroke	0.11-0.47 (Kristensen et al. 2013; Bernstein et al. 2008; Choi et	RR=1.37 (1.10-1.72) (Kristensen et al. 2013) IRR=1.32 (1.05-1.66) (Bernstein et al. 2008) HR=1.15 (1.07-1.24) (Sun et al. 2023) HR=1.18 (0.93-1.48) (Choi et al. 2019b)

Comorbidity	CD IR per 100 PY (or % as Indicated)	Effect Measures (95% Confidence Interval)
	al. 2019b; Sun et al. 2023; Tanislav et al. 2021)	HR=1.50 (1.10-2.06) (Tanislav et al. 2021)
Myocardial infarction	0.16-0.58 (Aniwan et al. 2018; Kristensen et al. 2013; Choi et al. 2019b)	HR=2.89 (1.65-5.13) (Aniwan et al. 2018) RR=1.35 (1.03-1.77) (Kristensen et al. 2013) HR=1.80 (1.47-2.21) (Choi et al. 2019b)
Thromboembolism		
Venous thrombo-embolism (VTE)	0.09-0.24 (Kappelman et al. 2011; Isene et al. 2014; Vegh et al. 2014)	HR=2.2 (2.0-2.5) (Kappelman et al. 2011) RR=1.08 (1.06-1.09) (Saleh et al. 2011) HR=1.74 (1.45-2.08) (Galloway et al. 2020)
Deep venous thrombosis (DVT)	0.13-0.31 (Kappelman et al. 2011; Bernstein et al. 2001a; Liu et al. 2021)	HR=1.9 (1.6-2.2) (Kappelman et al. 2011) IRR=4.71 (3.53-6.29) (Bernstein et al. 2001a) RR=1.24 (1.22-1.26) (Saleh et al. 2011)
Pulmonary embolism (PE)	0.06-0.11 (Kappelman et al. 2011; Bernstein et al. 2001a; Liu et al. 2021)	HR=2.9 (2.4-3.5) (Kappelman et al. 2011) IRR=2.94 (1.83-4.73) (Bernstein et al. 2001a)
Psychiatric Disorders		
Depression	0.38-2.48 (Bisgaard et al. 2023; Umar et al 2022; Ludvigsson et al. 2021; Choi et al. 2019a; Bernstein et al. 2019)	HR=1.7 (1.5-2.0) (Bisgaard et al. 2023) HR=1.36 (1.26-1.47) (Umar et al. 2022) HR= 1.5 (1.4-1.6) (Ludvigsson et al. 2021) HR=2.06 (1.74-2.44) (Choi et al. 2019a) IRR=1.76 (1.51-2.05) (Bernstein et al. 2019)
Suicide	0.03 (Ludvigsson et al. 2021)	HR=1.5 (1.2-1.9) (Ludvigsson et al. 2021)
Suicide attempts	0.89 (Ludvigsson et al. 2021)	HR=1.4 (1.3-1.4) (Ludvigsson et al. 2021)
Malignancies		
Overall	0.27-1.49 (Wu et al. 2023; Jess et al. 2013; Jung et al. 2017; So et al. 2017; Mizushima et al. 2010)	HR=1.15 (1.06-1.25) (Wu et al. 2023) SIR=2.17 (1.51-3.02) (Jung et al. 2017) SIR=1.55 (1.29-1.84) (Jess et al. 2013) SIR=0.93 (0.63-1.37) (So et al. 2017) SIR=2.2 (1.19-3.83) (Mizushima et al. 2010)
Small intestine	0.03 (Bernstein et al. 2001b)	IRR=17.4 (4.16-72.9) (Bernstein et al. 2001b)
Colon	0.13 (Bernstein et al. 2001b)	IRR=2.64 (1.69-4.12) (Bernstein et al. 2001b)
Lymphoma	0.05 (Bernstein et al. 2001b)	IRR=2.40 (1.17-4.97) (Bernstein et al. 2001b)
Hepatic Disorders		
NAFLD	10.95-53.80% (Kodali et al. 2023)	OR=2.79 (2.58-3.02) (Onwuzo et al. 2023)
PSC	0.58-3.4% (Burisch et al. 2019)	IRR=6.51 (2.86-14.85) (Burisch et al. 2019)
AIH	0.7% (Silva et al. 2019)	OR=2.7 (1.2-5.8) (Halling et al. 2017)

Comorbidity	CD IR per 100 PY (or % as Indicated)	Effect Measures (95% Confidence Interval)
Cholelithiasis	11-34% (Restellini et al. 2017)	HR=1.87 (1.34-2.61) (Chen et al. 2018)
Elevated liver enzymes	21.6% (Cappello et al. 2014)	ALT ≥2×ULN OR=1.70 (1.03-2.79) (Voss et al. 2021) GGT ≥2×ULN OR=1.49 (1.29-1.72) (Voss et al. 2021) GGT ≥5×ULN OR=3.01 (2.29-3.94) (Voss et al. 2021) ALP ≥2×ULN OR=3.81 (2.09-6.36) (Voss et al. 2021)
Other Autoimmune Disorders		
Rheumatoid arthritis	0.18 (Burisch et al. 2019)	IRR=3.59 (2.32-5.54) (Burisch et al. 2019) OR=2.1 (1.6-2.8) (Halling et al. 2017)
Ankylosing spondylitis	0.15 (Burisch et al. 2019)	IRR=14.71 (7.17-3.08) (Burisch et al. 2019) OR=11.7 (8.1-17.1) (Halling et al. 2017)
Celiac disease	0.05 (Burisch et al. 2019)	IRR=4.25 (1.91-9.49) (Burisch et al. 2019) OR=8.8 (5.9-13.0) (Halling et al. 2017)

Abbreviations: AIH = autoimmune hepatitis; ALP = alkaline phosphatase; ALT = alanine aminotransferase; CD = Crohn's disease; GGT = gamma-glutamyl transpeptidase; HR = hazard ratio; IR = incidence rate; IRR = incidence rate ratio; NAFLD = non-alcoholic fatty liver disease; OR = odds ratio; PSC = primary sclerosing cholangitis; PY = patient-years; RR = relative risk; SIR = standardised incidence rate; ULN = upper limit of normal.

Module SII – Non-clinical Part of the Safety Specification

SII.1 Toxicity

Key Issues Identified from Repeat-Dose Toxicity Studies

To assess the toxicity of mirikizumab and establish a margin of safety for clinical trials, a 4-week toxicity study and two 6-month toxicity studies in normal cynomolgus monkeys were conducted. The second 6-month study was conducted at higher doses compared to the prior studies to achieve higher systemic exposures. Safety pharmacology was evaluated as part of the 4-week study, and fertility was evaluated as part of the first 6-month study. The potential for effects on fertility was evaluated in sexually mature monkeys in the first 6-month study. The potential for effects on the developing foetus and on postnatal development was assessed in an ePPND study. The monkey is a pharmacologically relevant species for assessing non-clinical toxicity because mirikizumab binds with similar affinity to human and cynomolgus monkey IL-23 (21 pM and 55 pM, respectively).

The administration of mirikizumab to cynomolgus monkeys resulted in no adverse mirikizumab-related findings at weekly doses of 1 and 30 mg/kg SC, or 100 mg/kg IV for 4 weeks (with an 8-week recovery period), or at weekly doses of 10 and 100 mg/kg SC for 6 months. Therefore, the NOAEL was 100 mg/kg per week IV for the 4-week study and 100 mg/kg per week SC for the first 6-month study.

In the second, high-dose 6-month monkey study, the administration of mirikizumab twice weekly at doses of 100 mg/kg IV or 300 mg/kg IV (i.e., 200 or 600 mg/kg per week) resulted in no adverse findings considered related to neutralisation of IL-23. However, at the end of the 6-month dosing period, 1 monkey in the 600 mg/kg per week dose group had clinical laboratory and anatomic pathology findings without clinical signs that were indicative of an off-target idiosyncratic (i.e., low-incidence, non-dose responsive) immune-mediated haemolytic effect of mirikizumab administration. Therefore, in the second 6-month study, the NOAEL was 200 mg/kg per week IV. Off-target, immune-mediated safety findings in monkeys are generally not considered predictive of similar events in humans.

Reproductive Toxicity

The mirikizumab fertility assessment was conducted in the first 6-month repeat-dose toxicity study through the evaluation of reproductive organ weight and histopathology in sexually mature monkeys. No drug-related effects were observed in reproductive organ weights or in the histopathology of reproductive tissues from male or female monkeys after the 6-month treatment period.

The impact of mirikizumab on embryo-foetal development, pregnancy outcome, and peri- and postnatal development was assessed in an ePPND study in monkeys. Pregnant monkeys were administered mirikizumab at 300 mg/kg per dose twice weekly (i.e., 600 mg/kg per week) from Gestation Day 21 ± 1 until parturition. The infants were evaluated for up to 6 months following birth. There were no mirikizumab-related adverse effects (maternal, foetal, or infant).

SII.2 Safety Pharmacology

A safety pharmacology assessment performed during the 4-week monkey study included evaluation of cardiovascular safety, neurological safety, and specific vital signs. No drug-related changes occurred in any of these parameters.

SII.3 Other Toxicity-Related Information or Data

Local Tolerance

No adverse drug-related effects at IV or SC injection sites were observed in cynomolgus monkeys receiving mirikizumab.

Tissue Cross-Reactivity

No specific staining was observed in a full panel of tissues from normal human or monkey donors.

Carcinogenicity

Animal studies to assess the carcinogenic potential of mirikizumab have not been conducted. In accordance with ICH S1A and S6(R1) guidance (ICH 1995, 2011), Lilly has concluded that mirikizumab presents a low cancer risk to human patients based on:

- an assessment of published literature, which supports that neutralisation of IL-23 would not be expected to increase cancer risk,
- high selectivity against IL-23, with no off-target toxicity observed in toxicology studies,
- no evidence of increased cellular proliferation (hyperplasia or pre-neoplastic lesions) in toxicology studies, and
- no evidence of effects on cells or organ systems responsible for facets of tumour immunosurveillance (circulating lymphocytes, natural killer cell function, primary immune response, and lymphoid organ histopathology) in toxicology studies.

Conclusion

Based on the lack of toxicity at exposures exceeding the highest anticipated clinical exposures and lack of tissue cross-reactivity, the non-clinical safety profile of mirikizumab supports registration and continued clinical investigation. Mirikizumab resulted in no AEs in monkeys when administered once weekly (IV) for 4 weeks, once weekly (SC) for 6 months, or twice weekly (IV) for 6 months at doses of up to 100 mg/kg. Exposures associated with these dose levels provide margins of safety of 30-fold based on the induction dose of 300 mg IV and 100-fold at the maintenance dose of 200 mg SC for the UC indication and provide margins of safety of 8.7-fold based on the induction dose of 900 mg IV and 73-fold at the maintenance dose of 300 mg SC for the CD indication.

Module SIII - Clinical Trial Exposure

In this RMP, the safety of mirikizumab is evaluated in 4 integrated datasets:

- All Mirikizumab Exposures Integrated Analysis Set comprised of all clinical trial data in patients with UC, CD, and psoriasis treated with mirikizumab in completed and ongoing unblinded Phase 2 and 3 studies, and
- UC Mirikizumab Exposures Integrated Analysis Set comprised of all clinical trial data in patients with UC treated with mirikizumab in completed and ongoing unblinded studies.
- CD Mirikizumab Exposures Integrated Analysis Set comprised of all clinical trial data in patients with CD treated with mirikizumab in completed and ongoing unblinded studies.
- All IBD Mirikizumab Exposures Integrated Analysis Set comprised of all clinical trial data in patients with UC or CD treated with mirikizumab in completed and ongoing unblinded studies.

Table SIII.1. Duration of Exposure

All Miri Exposures Integrated Analysis Set	
Duration of exposure	**Patients**
>0 week to < 4weeks	51
≥4 weeks to <8 weeks	55
≥8 weeks to <12 weeks	79
≥12 weeks to <16 weeks	142
≥16 weeks to <24 weeks	150
≥24 weeks to <32 weeks	248
≥32 weeks to <52 weeks	278
≥52 weeks to <104 weeks	984
≥104 weeks	2815
Total number of patients	**4802**
Total patient-years for All Miri	**11003.1**
UC Miri Exposures Integrated Analysis Set	
Duration of exposure	**Patients**
>0 week to < 4weeks	10
≥4 weeks to <8 weeks	22
≥8 weeks to <12 weeks	32
≥12 weeks to <16 weeks	101
≥16 weeks to <24 weeks	44
≥24 weeks to <32 weeks	168
≥32 weeks to <52 weeks	47
≥52 weeks to <104 weeks	146
≥104 weeks	884
Total number of patients	**1454**
Total patient-years for UC	**3601.2**
CD Miri Exposures Integrated Analysis Set	
Duration of exposure	**Patients**
>0 week to <4 weeks	24
≥4 weeks to <8 weeks	23
≥8 weeks to <12 weeks	32
≥12 weeks to <16 weeks	29
≥16 weeks to <24 weeks	51
≥24 weeks to <32 weeks	43
≥32 weeks to <52 weeks	166
≥52 weeks to <104 weeks	456
≥104 weeks	354
Total number of patients	**1178**
Total patient-years for CD	**2004.2**

All IBD Miri Exposures Integrated Analysis Set	
Duration of exposure	**Patients**
>0 week to <4 weeks	34
≥4 weeks to <8 weeks	45
≥8 weeks to <12 weeks	64
≥12 weeks to <16 weeks	130
≥16 weeks to <24 weeks	95
≥24 weeks to <32 weeks	211
≥32 weeks to <52 weeks	213
≥52 weeks to <104 weeks	602
≥104 weeks	1238
Total number of patients	**2632**
Total patient-years for All IBD	**5605.4**

Abbreviations: CD = Crohn's disease; IBD = inflammatory bowel disease; miri = mirikizumab; UC = ulcerative colitis.

Source: /lillyce/prd/ly3074828/regulatory/subm_cd/output/shared/tfl/t_ex_expo_amiri_allm.rtf

Source: /lillyce/prd/ly3074828/regulatory/subm_cd/output/shared/tfl/t_ex_expo_amiri_allm_uc.rtf

Table SIII.2. Age Group and Gender

All Miri Exposures Integrated Analysis Set				
Age group	**Patients**		**Patient-years**	
	M	**F**	**M**	**F**
Adults (<65 years)	2814	1630	6592.9	3597.4
Elderly people	223	135	493.2	319.6
65-74 years	204	115	462.3	276.1
75-84 years	19	20	31.0	43.4
≥85 years	0	0	0	0
Total	**3037**	**1765**	**7086.2**	**3917.0**
UC Miri Exposures Integrated Analysis Set				
Age group	**Patients**		**Patient-years**	
Adults (<65 years)	819	528	2023.0	1335.2
Elderly people	60	47	123.6	119.4
65-74 years	55	41	117.5	109.0
75-84 years	5	6	6.0	10.4
≥85 years	0	0	0	0
Total	**879**	**575**	**2146.5**	**1454.7**
CD Miri Exposures Integrated Analysis Set				
Age group	**Patients**		**Patient-years**	
	M	**F**	**M**	**F**
Adults (<65 years)	621	519	1090.2	845.3
Elderly people	18	20	33.6	35.1
65-74 years	18	19	33.6	33.7
75-84 years	0	1	0	1.4
≥85 years	0	0	0	0
Total	**639**	**539**	**1123.8**	**880.4**
All IBD Miri Exposures Integrated Analysis Set				
Age group	**Patients**		**Patient-years**	
	M	**F**	**M**	**F**
Adults (<65 years)	1440	1047	3113.2	2180.5
Elderly people	78	67	157.2	154.6
65-74 years	73	60	151.1	142.7
75-84 years	5	7	6.0	11.9
≥85 years	0	0	0	0
Total	**1518**	**1114**	**3270.3**	**2335.1**

Abbreviations: CD = Crohn's disease; F = female; IBD = inflammatory bowel disease; M = male; miri = mirikizumab; UC = ulcerative colitis.

Source: /lillyce/prd/ly3074828/regulatory/subm_cd/output/shared/tfl/t_ex_expo_byagesex_amiri_allm.rtf

Table SIII.3. Dose

All Miri Exposures Integrated Analysis Set		
Dose of exposure	**Patients**	**Patient-years**
30 mg PRN SC	15	21
30 mg Q8W SC	51	15.4
50 mg Q4W IV	63	15.0
100 mg PRN SC	30	40.9
100 mg Q8W SC	51	15.7
125 mg Q8W SC	559	1149.0
200 mg Q12W SC	46	65.8
200 mg Q4W IV	93	28.2
200 mg Q4W SC	1091	3085.1
250 mg Q8W SC	1750	3383.4
250 mg Q4W SC	1572	507.0
300 mg PRN SC	34	52.0
300 mg Q8W SC	165	213.2
300 mg Q4W IV	1135	377.3
300 mg Q4W SC	1070	1637.3
600 mg Q4W IV	118	35.2
900 mg Q4W IV	857	248.8
1000 mg Q4W IV	237	112.8
Total	**4802**	**11003.1**
UC Miri Exposures Integrated Analysis Set		
Dose of exposure	**Patients**	**Patient-years**
50 mg Q4W IV	63	15.0
200 mg Q12W SC	46	65.8
200 mg Q4W IV	62	14.8
200 mg Q4W SC	1091	3085.1
300 mg Q4W IV	1135	377.3
600 mg Q4W IV	86	21.7
1000 mg Q4W IV	96	21.6
Total	**1454**	**3601.2**
CD Miri Exposures Integrated Analysis Set		
Dose of exposure	**Patients**	**Patient-years**
200 mg Q4W IV	31	13.4
300 mg Q4W SC	1070	1637.3
600 mg Q4W IV	32	13.5
900 mg Q4W IV	857	248.8
1000 mg Q4W IV	141	91.3
Total	**1178**	**2004.2**

All IBD Miri Exposures Integrated Analysis Set		
Dose of exposure	**Patients**	**Patient-years**
50 mg Q4W IV	63	15.0
200 mg Q12W SC	46	65.8
200 mg Q4W IV	93	28.2
200 mg Q4W SC	1091	3085.1
300 mg Q4W IV	1135	377.3
300 mg Q4W SC	1070	1637.3
600 mg Q4W IV	118	35.2
900 mg Q4W IV	857	248.8
1000 mg Q4W IV	237	112.8
Total	**2632**	**5605.4**

Abbreviations: CD = Crohn's disease; IBD = inflammatory bowel disease; IV = intravenous; miri = mirikizumab; PRN = as needed; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SC = subcutaneous; UC = ulcerative colitis.

Source: /lillyce/prd/ly3074828/regulatory/subm_cd/output/shared/tfl/t_ex_expo_bytrtdos_amiri_allm.rtf

Table SIII.4. Race

Ethnic origin	Patients	Patient-years
All Miri Exposures Integrated Analysis Set		
American Indian or Alaska Native	83	197.0
Asian	986	2123.8
Black or African American	87	208.7
Native Hawaiian or other Pacific Islander	5	9.6
White	3603	8407.3
Multiple	14	27.5
Missing	24	29.1
Total	**4802**	**11003.1**
UC Miri Exposures Integrated Analysis Set		
American Indian or Alaska Native	11	18.4
Asian	308	700.9
Black or African American	19	50.6
Native Hawaiian or other Pacific Islander	1	2.3
White	1102	2811.8
Multiple	3	3.8
Missing	10	13.4
Total	**1454**	**3601.2**
CD Miri Exposures Integrated Analysis Set		
American Indian or Alaska Native	5	7.7
Asian	243	373.7
Black or African American	29	68.8
Native Hawaiian or other Pacific Islander	0	0
White	883	1530.2
Multiple	5	9.2
Missing	13	14.7
Total	**1178**	**2004.2**
All IBD Miri Exposures Integrated Analysis Set		
American Indian or Alaska Native	16	26.0
Asian	551	1074.6
Black or African American	48	119.4
Native Hawaiian or other Pacific Islander	1	2.3
White	1985	4342.0
Multiple	8	13.0
Missing	23	28.1
Total	**2632**	**5605.4**

Abbreviations: CD = Crohn's disease; IBD = inflammatory bowel disease; miri = mirikizumab; UC = ulcerative colitis.

Source: /lillyce/prd/ly3074828/regulatory/subm_cd/output/shared/tfl/t_ex_expo_byrace_amiri_allm.rtf

Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Criteria: Patients below 18 years of age

Reason for exclusion: The safety and efficacy for patients below 18 years of age have not been established. To establish the efficacy and safety of this molecule, Phase 3 clinical trials were conducted first in adults. One Phase 2 clinical trial in paediatric patients with UC aged 2 to less than 18 years is completed, and 2 Phase 3 studies in paediatric patients aged 2 to less than 18 years are ongoing (1 in paediatric patients with UC and 1 in paediatric patients with CD).

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

Rationale: Section 8.4 of the prescribing information for UC states that the safety and efficacy of mirikizumab have not been established in paediatric patients. Additionally, approved, alternative therapeutic options are available for the treatment of UC or CD in paediatric patients. It was agreed with Regulatory Agencies (US and EU) to start paediatric development once a positive risk-benefit in adults had been established.

Criteria: Women who are pregnant or lactating

Reason for exclusion: This is a standard exclusion criterion in clinical development. Although there were no adverse effects on the embryos, foetuses, and offspring demonstrated in non-clinical studies using pregnant monkeys, insufficient information on the effects of mirikizumab on maternal health or the foetus prohibited the inclusion of pregnant women in the development programme. Women of childbearing potential are expected to comprise a significant proportion of the target UC or CD population. There were 36 pregnancies from maternal exposure and 52 pregnancies from paternal exposure reported during the clinical development programme.

Is it considered to be included as missing information? Yes

Rationale: Not applicable

Criteria: Serious infection, herpes zoster infection (current or past), TB, positive test for HBV or HCV

Reason for exclusion: These criteria excluded individuals with previous or concomitant serious infections that may have increased the risk for safety observations if allowed participation in the study based on theoretical concerns and to minimise confounding factors in data interpretation.

Is it considered to be included as missing information? No

Rationale: While there are insufficient data on the safety of mirikizumab in the above-mentioned subpopulations, per international guidelines on good clinical practices, these patients should not initiate treatment with immunosuppressive/immunomodulatory agents. The prevalence of these conditions in the target population is anticipated to be low. However, in line with the SmPC special warnings and precautions for use, treatment with mirikizumab should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. A contraindication in Section 4.3 instructs that patients with clinically important active infections (active TB) should not take mirikizumab. The risks and benefits of treatment prior to initiating the use of mirikizumab in patients with a chronic infection or a history of recurrent infection should be considered. Patients should be instructed to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a serious infection develops, discontinuation of mirikizumab should be considered until the infection resolves.

Patients with current or recent serious infection, current herpes zoster or history, positive HBV or HCV, and active TB were excluded from the studies. However, infectious events occurred during the clinical programme, and clinical data are now available to provide the basis of label recommendations as described in the SmPC.

Criteria: Exposure to or receipt of a live vaccine

Reason for exclusion: While there are insufficient data on the safety of mirikizumab in patients receiving live vaccines, per international guidelines on good clinical practices, administration of live vaccines is not recommended in patients treated with immunosuppressive/ immunomodulatory agents due to the potential impact those agents may have on the development of protective antibody responses to the vaccine, increasing the risk for infective complications. In line with the SmPC special warnings and precautions for use, the use of live vaccines in patients treated with mirikizumab should be avoided. No data are available on the response to live or non-live vaccines in patients treated with mirikizumab.

Is it considered to be included as missing information? No

Rationale: Live vaccines were not studied in patients receiving mirikizumab, and concomitant administration is not recommended. In line with the SmPC, it is recommended that live vaccines should not be administered concurrent with receiving mirikizumab.

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 or adverse reactions with a long latency.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table SIV.1. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Pregnancy was an exclusion criterion in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patients with relevant comorbidities: Patients with hepatic impairment Patients with renal impairment Patients with cardiovascular impairment	Mirikizumab has not been specifically studied in patients with renal, hepatic or cardiovascular impairment.
Immunocompromised patients	Immunocompromised patients were excluded from mirikizumab clinical trials
Patients with a disease severity different from inclusion criteria in clinical trials	The clinical development programme included adult patients with moderately to severely active UC or CD. Patients with mild disease were not specifically studied.
Population with relevant different ethnic and racial origin	Mirikizumab Phase 3 clinical trials enrolled patients with psoriasis, UC, and CD globally. Patients of non-White origin were included in the clinical trials. Of the treated population, 18.0% were Hispanic or Latino, 81.3% were non-Hispanic/non-Latino, and ethnicity data were missing for 0.6%; 75.0% were White or Caucasian, 20.5% were Asian, 1.7% were American Indian or Alaskan natives, 1.8% were Black or African American, 0.3% reported multiple races, and 0.1% were native Hawaiians or Pacific Islanders. Race data were missing for 0.5%. Although there were few Black or African American participants in the mirikizumab studies, the distribution of patients of different racial origins is generally reflective of the anticipated target population. There have been no significant differences in tolerability, safety, and efficacy profiles with regard to racial and/or ethnic origin observed with mirikizumab treatment in clinical studies.
Subpopulations carrying relevant genetic polymorphisms	Not applicable. Patient-level genetic polymorphisms were not specifically studied in the clinical development programme.

Type of special population	Exposure
Elderly	Mirikizumab clinical trials enrolled patients 85 years and younger in age, including 6.6% aged 65 to 74 years, and 0.8% aged 75 to 84 years. Patients older than 85 years of age were not included in mirikizumab clinical trials. The available data do not suggest meaningful difference in safety between age categories to warrant considerations based on age.
Other	Not applicable

Abbreviations: CD = Crohn's disease; UC = ulcerative colitis.

Module SV - Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

Worldwide sales of mirikizumab have been collected for the cumulative time period through 31 August 2023.

SV.1.2 Exposure

As of 31 August 2023, there has been 3 390 600 mg of mirikizumab sold worldwide. Table SV.1 provides a geographical summary of mirikizumab sales.

Table SV.1. Geographical Summary of Sales of Mirikizumab

Region	Sales Ex -factory (Milligrams)
Europe	134 500
Japan	3 256 100
Global total	3 390 600

The number of patients cannot be adequately estimated at this time due to small-volume sales and the limited period of market availability. It should also be noted that the early sales of a newly marketed product may often reflect stocking by wholesalers as opposed to actual consumption by patients. Trending sales data across several periodic report periods will give an indication of the true level of use of the product in the patient population.

Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 - Potential for Misuse for Illegal Purposes

The potential for misuse for illegal purposes is not anticipated based on the mechanism of action, lack of adverse reactions associated with mood or mind alterations, and no findings that mirikizumab causes physical or mental dependency. Furthermore, mirikizumab induction therapy as IV infusion is administered in the health care setting and, therefore, a potential for misuse for illegal purposes is not anticipated. Based on pack sizes, which vary by geography, the potential for misuse for illegal purpose is additionally minimised.

Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated): None.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated: None.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers:

- Upper respiratory tract infections: Upper respiratory tract infections have been reported commonly and require no further characterisation beyond routine pharmacovigilance activities and product labelling.
- Injection site reactions: Injection site reactions have been reported commonly and require no further characterisation beyond routine pharmacovigilance activities and product labelling.
- Rash: Rash has been reported commonly and require no further characterisation beyond routine pharmacovigilance activities and product labelling.
- Headache: Headache has been reported commonly and requires no further characterisation beyond routine pharmacovigilance activities and product labelling.
- Arthralgia: Arthralgia has been reported commonly and requires no further characterisation beyond routine pharmacovigilance activities and product labelling.
- Herpes zoster: Herpes zoster has been reported uncommonly and requires no further characterisation beyond routine pharmacovigilance activities and product labelling.
- Infusion-related hypersensitivity reaction: Infusion-related reactions have been reported uncommonly and require no further characterisation beyond routine pharmacovigilance activities and product labelling.
- Infusion site reaction: Infusion site reaction has been reported uncommonly and requires no further characterisation beyond routine pharmacovigilance activities and product labelling.

Known risks that do not impact the risk-benefit profile: None.

Other reasons for considering the risks not important: None.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risks: None

Important Potential Risk 1: Serious Infections

Risk-benefit impact:

Although there was no imbalance for infections in patients treated with mirikizumab compared to placebo across the datasets, exposure is limited to the clinical trial population. Patients with active, chronic, recurring, and/or opportunistic infections were excluded from the mirikizumab clinical trials, and the potential for the development of serious recurrent or reactivated infections in a larger population or with longer exposures to mirikizumab is unknown at this time.

In patients with UC in the Phase 2 and Phase 3 studies, serious infections were reported commonly during treatment with mirikizumab. Of the 33 serious infections, the most frequently reported were pneumonia (15.2%) and appendicitis (12.1%), and none was a reactivated infection. When including time off mirikizumab and the post-treatment follow-up time, serious infections were also reported commonly. Although the majority of patients recovered, serious infections due to COVID-19/coronavirus infection or sequelae of COVID-19 infection resulted in the deaths of 1 patient while receiving mirikizumab and 2 patients while off mirikizumab. One patient with UC discontinued mirikizumab due to a serious infection of pneumonia and recovered without an adverse clinical outcome.

Across all mirikizumab exposures in Phase 2 and Phase 3 clinical trials for UC, CD, and psoriasis, serious infections were reported commonly during treatment with mirikizumab. When including time off mirikizumab and the post-treatment follow-up time, serious infections were also reported commonly. Although the majority of patients recovered, serious infections due to COVID-19/coronavirus infection or sequelae of COVID-19 infection resulted in the deaths of 7 patients, 5 while receiving mirikizumab (1 patient with UC as described above and 4 patients with psoriasis) and 2 while off mirikizumab (both patients with UC, as described above). Ten patients in this dataset discontinued mirikizumab due to their serious infection, including the 5 patients who died as previously described and 5 who recovered or were recovering without adverse clinical outcomes.

Important Potential Risk 2: Severe Liver Injury

Risk-benefit impact:

In patients with UC in the Phase 2 and Phase 3 studies, severe hepatic AEs were reported uncommonly (n = 3, 0.2%), none of which were reported as an SAE. One patient with UC met Hy's law criteria with a maximum ALT ≥3×ULN and maximum total bilirubin ≥2×ULN and no alternative aetiology for the elevations based on the reported information. Taking into consideration the available information, this case was assessed as a probable DILI. Three patients with UC discontinued mirikizumab due to a hepatic TEAE, AIH (n = 1, 0.1%) and

hepatic enzyme increased (n = 2, 0.1%), which resolved or were resolving without adverse clinical outcomes.

Across all mirikizumab exposures in Phase 2 and Phase 3 clinical trials for UC, CD, and psoriasis, severe hepatic AEs were reported uncommonly (n = 18, 0.5%), 2 of which were also reported as SAEs. Fourteen patients across the clinical development programme discontinued mirikizumab due to a treatment-emergent hepatic event. Of these, 13 discontinued due to increased or abnormal liver function tests/enzymes (n = 12) and increased ALP (n = 1), which resolved without adverse clinical outcomes. Confounding factors for the patients who discontinued mirikizumab due to a treatment emergent hepatic event include concomitant medications with known adverse effects on the liver, past and current alcohol use, and medical conditions, including sclerosing cholangitis, alcoholic liver disease, hepatitis A, hepatitis D, hepatitis E, hyperbilirubinemia, NAFLD, latent TB, increased AST, TB, and unspecific abnormal hepatic function and liver disorder.

Hepatic enzyme elevations, specifically ALT and AST, are uncommon ADRs for mirikizumab based on numeric differences in patients with elevated ALT ≥5×ULN treated with mirikizumab compared to placebo (0.8% and 0%, respectively, in Study AMBG) and AST ≥5×ULN treated with mirikizumab compared to placebo (0.2% and 0%, respectively, in Study AMAN and 0.8% and 0%, respectively, in Study AMBG).

Important Potential Risk 3: Malignancies

Risk-benefit impact:

Some studies have found that UC is associated with an increased risk of cancer relative to the general population (Karlén et al. 1999; Jussila et al. 2013; Jung et al. 2017; Burisch et al. 2022). As such, the observed rate of malignancies seen in the mirikizumab-treated population in the clinical development program is considered to reflect the presence of this co-morbidity in the target population rather than a potential effect of the drug. In the UC clinical development programme, the IRs for malignancies overall and specifically for cancer of the rectum, colon cancer, prostate cancer, and NMSC were consistent with the reported background IRs in the UC population.

Current clinical and non-clinical data do not suggest a causal association between mirikizumab and malignant tumours. Malignancy events are events of long latency and thus, the potential for development with longer exposures to mirikizumab is unknown at this time with limited duration of exposure. However, the benefits of mirikizumab to patients with moderately to severely active UC are believed to outweigh any potential risk of malignancy.

Important Potential Risk 4: MACE

Risk-benefit impact:

Cardiovascular disorders are known, important co-morbidities in the UC population. Based on cumulative data across the mirikizumab clinical development program, the IR of MACE (IR=0.2) is below the range of the background IR in the UC population (1.1 IR), and moderate-to-severe psoriasis population (0.4 to 1.5 IR) and within rates for other IL-23p19 inhibitors (IR=0.2 to 0.6) approved for the treatment of psoriasis. Current clinical and non-clinical data do not suggest a causal association between mirikizumab and MACE. MACE are rare events. Thus, the potential for development with larger and longer exposures to mirikizumab is unknown at this time with limited duration of exposure. However, the benefits of mirikizumab to patients with moderately to severely active UC are believed to outweigh the potential risk of MACE.

Missing information 1: Safety of mirikizumab in pregnant women and lactating women.

Risk-benefit impact:

The current data are too limited to draw conclusions about the effect of mirikizumab exposure during pregnancy in humans, and no data are available to assess the safety of mirikizumab in lactating women.

No adverse effects were noted on reproductive organs or tissues in young adult or sexually mature male or female monkeys at any dose tested in all studies. In ePPND study in monkeys, there were no mirikizumab-related adverse effects (maternal, foetal, or infant) at the dose level tested.

Pregnant women were excluded from entering mirikizumab clinical studies. Women of childbearing potential agreed to comply with protocol-specified contraceptive requirements, and male participants were not required to use contraception. Pregnancy occurring in female clinical trial participants was a criterion for permanent discontinuation of mirikizumab in all studies, and pregnant participants and partner pregnancies who consented are followed to pregnancy completion.

Across all indications, there are limited safety data on the use of mirikizumab in pregnant women treated with mirikizumab. To date, of the 1316 females exposed to mirikizumab, 28 have become pregnant, and the outcomes of these pregnancies are provided below:

Outcome	No. of Events (n)	Percent (%) of Total Female Exposure (n/28)
Normal outcome	7	25%
Elective abortion[a]	6	21%
Spontaneous abortion	3	11%
Unknown as lost to follow-up[b]	4	14%
Still in utero at data cutoff	7	25%
Premature birth	1	4%

Abbreviation: n = number of participants within each specific category

a One case of elective abortion was reported in a healthy volunteer.

b One case of pregnancy with an unknown outcome was reported in a healthy volunteer.

Developmental toxicity studies in pregnant monkeys revealed no evidence of harm to the foetus or infant. Labels will reflect that there are insufficient human data to establish the safety of mirikizumab during pregnancy. As a precautionary measure, it is preferable to avoid the use of mirikizumab during pregnancy. Women of childbearing potential should use an effective method of contraception during treatment and for at least 10 weeks after treatment.

It is not known whether mirikizumab is excreted in human milk or absorbed systemically after ingestion. Administer mirikizumab to nursing women only if the potential benefit to the mother justifies the potential risk to the infant.

Although the risk of mirikizumab to pregnant women with UC is not expected to be different, mirikizumab use during pregnancy is considered missing information. Therefore, an observational database study in a larger population than in clinical development will be conducted because of the limited data on pregnancy outcomes. Should emerging experience of use in pregnancy reveal clinically relevant adverse outcomes to the mother, foetus, and/ or baby, this could have an impact on the benefit-risk of mirikizumab use in female patients with UC.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risks: None

Important Potential Risk 1: Serious Infections

Potential mechanisms:

Mirikizumab is a humanised, immunoglobulin-4, monoclonal, anti-IL-23 antibody that binds with high affinity and specificity to the p19 subunit of human IL-23 cytokine and inhibits its interaction with the IL-23 receptor. IL-23 induces T-lymphocyte-type TH17 response, which is responsible for fighting extracellular infections. Depending on the cytokine environment, TH17 response may also activate TH1 response, which is responsible for fighting intracellular infections. Blocking IL-23 may reduce TH17 and TH1 responses and potentially increase the risk of infections.

Evidence source(s) and strength of evidence:

In participants with IBD across the Phase 2 and Phase 3 studies for UC and CD, serious infections (n = 76, 2.9%, EAIR [per 100 patient-years of exposure] 1.4) were reported commonly during treatment with mirikizumab. When including time off mirikizumab (defined as the time from mirikizumab discontinuation to either study discontinuation or, in the case of the Phase 3 UC maintenance study, the resumption of mirikizumab in mirikizumab responders who were re-randomised to placebo), serious infections (n = 82, 3.1%, EAIR 1.4) were also reported commonly, which is unchanged from the EAIR and frequency category of serious infections reported during treatment with mirikizumab.

Although the majority of participants with IBD who reported serious infections recovered, recovered with sequelae, or were recovering, serious infections resulted in the death of 6 participants with IBD.

Characterisation of the risk:

Serious infections were those that met the criteria of an SAE.

Placebo-controlled induction exposures:

UC:

In the placebo-controlled induction study, the frequency of serious infections was similar for participants who received mirikizumab (0.7%) compared to participants who received placebo (0.6%).

CD:

In the placebo-controlled induction period of study, the frequency of serious infections was similar for participants who received mirikizumab (1.1%) compared to participants who received placebo (0.5%).

All IBD exposures:

In the IBD exposures in the Phase 2 and Phase 3 clinical trials for UC and CD (N = 2632), serious infections (n = 76, 2.9%, EAIR 1.4) were reported commonly in participants during treatment with mirikizumab. Serious infections (n = 82, 3.1%, EAIR 1.4) were also reported commonly when including time off mirikizumab (defined as the time from mirikizumab discontinuation to either study discontinuation or, in the case of the Phase 3 UC maintenance study, the resumption of mirikizumab in mirikizumab responders who were re-randomised to placebo).

The most frequently reported serious infections during treatment with mirikizumab were

- pneumonia (n = 10, 0.4%)
- COVID-19 (n = 9, 0.3%)
- COVID-19 pneumonia (n = 5, 0.2%)
- appendicitis (n = 6, 0.2%), and
- sepsis (n = 4, 0.2%).

All other serious infections were reported at a frequency of 0.1% or less.

When including the time off mirikizumab, the most frequently reported serious infections were consistent, with no additional types of serious infections.

Five deaths from coronavirus or COVID-19 infections were reported in the IBD population (4 in participants with UC and 1 in a participant with CD). Of these deaths, 3 participants were on mirikizumab at the time of their death, and the other 2 deaths occurred when the participants were off mirikizumab.

One additional death was reported in a participant with UC due to disseminated intravascular coagulation secondary to sepsis and subsequently adjudicated as a death due to infection, which occurred when the participant was off mirikizumab after receiving mirikizumab in the induction study.

All mirikizumab exposures:

In all mirikizumab exposures in Phase 2 and Phase 3 clinical trials for UC, CD, and psoriasis (N = 4802), serious infections (n = 142, 3.0%, EAIR 1.3) were reported commonly in participants during treatment with mirikizumab.

The most frequently reported serious infections during treatment with mirikizumab were consistent with those reported for the IBD data above with no substantial change in either type or frequency of serious infections.

In addition to the deaths of participants with IBD described above, 4 participants with psoriasis died from COVID-19 infection or sequelae of this infection while receiving mirikizumab in the long-term extension study. No other deaths from serious infections were reported in participants with psoriasis.

Eight of the 9 deaths due to coronavirus or COVID-19 infection or sequelae of COVID-19 infection in the mirikizumab programme (4 participants with psoriasis and 4 participants with UC) occurred early in the COVID-19 pandemic, prior to the availability of effective treatments and vaccinations. One death that occurred when effective treatments and vaccinations were available was in a participant with CD who was not vaccinated for COVID-19. All participants with fatal COVID-19 infections were at increased risk of hospitalisation, severe disease, and death due to COVID-19 based on one or more of the following criteria (Zhou et al. 2020):

- age greater than 65 years (Mueller et al. 2020)
- smoking (Reddy et al. 2021)
- obesity
- diabetes mellitus
- cardiovascular disease
- hypertension
- liver disease, and/or
- malignancy (Zhou et al. 2020).

None of these deaths from severe COVID-19/coronavirus infection or sequelae of COVID-19 infection were determined by the investigator or sponsor to be related to mirikizumab.

Risk factors and risk groups:

Risk groups or specific risk factors for serious infections have not been identified from the clinical development programme. Due to the immunomodulatory effect of medicines in the anti-IL-23 class, patients with evidence of untreated latent TB or other active, chronic, or recurrent infections or a history thereof may be at greater risk of reactivation or exacerbation of their underlying infection, even though this has not been reported in the mirikizumab clinical development programme.

Preventability:

Careful monitoring of patients for early detection of signs of infection and application of appropriate intervention may help to prevent infections from becoming serious. The monitoring of patients in this clinical development programme may have helped with the early detection of infections and may have contributed to recovery from their serious infections for the majority of patients. Label language on infections raises awareness regarding this risk, aimed for similar outcomes in the post-marketing phase. With the availability of COVID-19 vaccinations and medications, the frequency of severe COVID-19 infections and sequalae has decreased, and outcomes have improved (Moghadas et al. 2021; Zhang et al. 2021; Lee et al. 2023).

The label warns that mirikizumab should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. The risks and benefits of treatment should be considered prior to initiating use of mirikizumab in patients with a chronic infection or a history of recurrent infection. The label also warns that mirikizumab should not be given to patients with active TB, and anti-TB therapy should be considered before starting mirikizumab in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. The label states that patients receiving mirikizumab should be monitored for signs and symptoms of active TB during and after treatment.

Impact on the risk-benefit balance of the product:

The current impact of serious infections on the risk-benefit balance of mirikizumab is considered to be low. This assessment is based on the cumulative exposures across the psoriasis, UC, and CD treatment groups, which includes 4802 participants (11003.1 PYE) in total, 2632 of whom were participants with IBD (5605.4 PYE), and the EAIR of serious infections in mirikizumab-treated participants was 1.3 (1.4 in IBD). Although serious infections were reported commonly in both data sets, the majority of participants recovered or were recovering without sequelae or adverse clinical outcomes. Most serious infections were due to COVID-19 infections or sequelae of COVID-19 and occurred early in the global pandemic, prior to the availability of effective treatment and/or vaccinations and in participants with 1 or more risk factors for adverse clinical outcomes. Since that time, effective vaccinations and treatments for COVID-19 have become available.

Patients with UC and CD are considered to be at an increased risk of infection due to the underlying condition and important possible comorbidities with an inherent risk of infections and/or prevalent use of concomitant immunosuppressive therapy. Given that an association between immunomodulatory and/or immunosuppressive therapy and infection is known to treating physicians, it is expected that infections are readily diagnosed and managed in clinical care.

Therefore, the impact of serious infections on the risk-benefit balance is considered low, and labelling is expected to mitigate the potential risk of serious infections.

Public health impact:

Mirikizumab is indicated for a defined subset of the population with moderately to severely active UC and is proposed for the population with moderately to severely active CD. In participants with IBD in the Phase 2 and Phase 3 clinical trials, the frequency of serious infections during treatment with mirikizumab was low, and the majority of participants recovered with no sequalae. The impact of serious infections on public health is considered to be low.

Important Potential Risk 2: Severe Liver Injury

Potential mechanisms:

Elevated liver enzymes and hepatic comorbidities, including NAFLD, PSC, AIH, and cholelithiasis, have been observed in participants with IBD. No biological mechanism to explain

the observed increases in ALT and AST levels has been identified in the context of mirikizumab treatment, and no adverse hepatic effects were observed in the non-clinical studies.

Evidence source(s) and strength of evidence:

For the IBD population exposed to mirikizumab in the Phase 2 and Phase 3 clinical trials, elevated ALT ≥5×ULN and ≥10×ULN were reported by 0.7% and 0.2% of participants in the mirikizumab treatment group respectively. Elevated AST ≥5×ULN and ≥10×ULN were reported by 0.8% and 0.1% of participants in the mirikizumab treatment group, respectively.

For all mirikizumab exposures in Phase 2 and Phase 3 clinical trials for UC, CD, and psoriasis, elevated ALT and AST ≥10×ULN was reported for each analyte in 0.2% of mirikizumab-treated participants.

Most of these liver enzyme elevations/increases were considered mild to moderate in severity and 3 participants with psoriasis had AST and or ALT elevations that were reported as serious. None were associated with an adverse clinical outcome. Overall, 0.3% of participants discontinued due to a TEAE of liver enzyme elevation. Most recovered from the liver enzyme elevations while continuing on mirikizumab treatment and with no further adverse effects.

One mirikizumab treatment participant with UC met Hy's law criteria with a maximum ALT of 17.9×ULN, maximum AST of 9.9×ULN, and maximum bilirubin of 2.4×ULN. This TEAE of "hepatic enzyme increased" was reported as moderate severity and as non-serious. As no alternative aetiology for liver function tests LFT elevation could be determined, an association with mirikizumab treatment could not be excluded. Therefore, based on the potential of significantly elevated aminotransferases being indicative of possible severe liver injury, it is considered an important potential risk.

Characterisation of the risk:
Placebo-controlled induction exposures:

UC:

In the placebo-controlled induction study,

- the percentages of participants reporting at least 1 narrow scope hepatic TEAE were low and similar between the treatment groups (1.6% in both mirikizumab and placebo) nearly all events were mild to moderate in severity, and there were no SAEs or discontinuations due to a hepatic TEAE
- ALT or AST shifts to ≥3×ULN or ≥5×ULN were reported in a small number of participants (≤1%)
- no ALT or AST shifts to ≥10×ULN were reported, and
- most elevations in aminotransferases were resolved without mirikizumab discontinuation.

CD:

In the placebo-controlled induction period,

- the frequency of participants reporting at least 1 narrow scope hepatic TEAEs were lower for patients who received mirikizumab (1.9%) compared to participants who received placebo (2.8%)
- nearly all events were mild to moderate in severity, there were no SAEs, and few participants discontinued treatment due to such an event
- ALT or AST shifts to ≥3×ULN or ≥5×ULN were reported in a small number of participants (≤0.5%)
- no ALT or AST shifts to ≥10×ULN were reported
- most elevations in aminotransferases were resolved without mirikizumab discontinuation, and
- the frequency and EAIRs of the TEAEs ALT increased and AST increased were numerically higher in the mirikizumab treatment participants compared to placebo group participants:
    - the PT of *ALT increased* was reported in 1.0% (EAIR 4.0) of mirikizumab treatment participants compared with 0.5% (EAIR 2.0) of placebo group participants, and
    - the PT of *AST increased* was reported in 0.3% (EAIR 1.3) of mirikizumab treatment participants compared with 0 placebo participants.

All IBD exposures:

In the IBD population exposed to mirikizumab in the Phase 2 and Phase 3 clinical trials for UC and CD,

- 173 participants (6.6%, EAIR 3.3) reported at least 1 narrow scope hepatic TEAE
- 2 (0.1%) participants reported a hepatic SAE (n=1 for transaminase increased and liver disorder)
- 7 (0.3%) participants discontinued mirikizumab due to a hepatic TEAE, of which 5 (0.2%) were due to TEAE hepatic enzyme elevations
- 4 (0.2%) participants with IBD reported a severe hepatic TEAE, none of which resulted in discontinuation of mirikizumab, and 3 (0.1%) were reported as recovered, recovered with sequelae, or recovering, and
- in the IBD population, the EAIRs of ALT and AST shifts to at least 3-fold ULN, at least 5-fold ULN, and at least 10-fold ULN were low (less than or equal to 1.1) and did not suggest an increase in ALT and AST shifts with increased exposure and duration of mirikizumab treatment.

All mirikizumab exposures:

In all mirikizumab exposures in Phase 2 and Phase 3 clinical trials for UC, CD, and psoriasis,

- 349 participants (7.3%, EAIR 3.3) reported at least 1 narrow scope hepatic TEAE, of which 5 (0.1%, EAIR 0.05) were reported as serious (2 in participants with IBD and 3 in participants with psoriasis)
- 17 (0.4%) participants discontinued mirikizumab due to at least 1 narrow scope hepatic TEAE, and
- 19 (0.4%) participants (4 with IBD and 15 with psoriasis) reported a severe TE hepatic AE, of which 3 (0.1%) resulted in the discontinuation of mirikizumab and 16 (0.3%) were reported as recovered, recovered with sequelae, or recovering.

The EAIRs of ALT and AST shifts to at least 3-fold ULN, at least 5-fold ULN, and at least 10-fold ULN were also low (less than or equal to 1.3) and stable with the increasing duration of mirikizumab exposure. Although most participants recovered from the hepatic enzyme elevations while continuing on mirikizumab, 15 participants (0.3%) discontinued due to TEAE of hepatic enzyme elevations.

Risk factors and risk groups:

In the UC, CD, and psoriasis programmes, no specific risk groups or specific risk factors have been identified, although concurrent use of alcohol or medications, or both, with a known risk of hepatic enzyme elevation or DILI may result in a higher frequency of hepatic enzyme elevations and possible liver injury. Additionally, clinical observations of transient elevations of hepatic enzymes with no known cause, persistent elevations most commonly due to PSC, AIH, cholelithiasis, and NAFLD, and the use of some herbal, dietary, and traditional healing and supplemental products may also contribute to a higher frequency of hepatic enzyme elevations and possible liver injury. In the IBD programme, no specific risk factors have been identified.

Preventability:

As no risk groups or risk factors have been identified, elevations in hepatic enzymes are unlikely to be preventable. Early detection of hepatic enzyme elevations and application of an appropriate intervention may help to prevent outcomes from becoming serious. Therefore, the label monitoring guidance states that liver enzymes and bilirubin should be evaluated at baseline and monthly during induction (including extended induction period, if applicable). Thereafter, liver enzymes and bilirubin should be monitored (every 1 to 4 months) according to standard practice for patient management and as clinically indicated. If increases in ALT or AST are observed and DILI is suspected, mirikizumab must be discontinued until this diagnosis is excluded.

Alanine aminotransferase increased and aspartate aminotransferase increased are adverse drug reactions for mirikizumab, and the warning and precaution language advises that if increases in ALT or AST are observed and drug-associated liver injury is suspected, mirikizumab must be discontinued until this diagnosis is excluded.

Impact on the risk-benefit balance of the product:
Among the hepatic AEs reported in all mirikizumab exposures in Phase 2 and Phase 3 clinical trials for IBD and psoriasis, the majority were mild to moderate in severity and did not result in discontinuation of mirikizumab. No AEs of treatment-emergent DILI related to mirikizumab were reported. One case meeting Hy's law criteria had rapid resolution of liver enzymes upon discontinuation of mirikizumab.

Based on the available clinical data, the current impact on the risk-benefit balance of mirikizumab is considered low, and labelling informs prescribers of the potential risk of severe liver injury.

Public health impact:
Mirikizumab is indicated for a clearly defined subset of the population with moderately to severely active UC and proposed for a clearly defined subset of the population with moderately to severely active CD, and the impact of severe liver injury on public health is considered to be low.

Important Potential Risk 3: Malignancies

Potential mechanisms:

IL-23 expression or overexpression is observed in several human tumour types and is, in many cases, associated with a poorer prognosis. The pro-tumour effects of IL-23 are attributable to mechanisms including stimulation of inflammatory cell-derived cytokines, chemokines, and growth factors, evasion of immune surveillance, the promotion of angiogenesis, and increased invasive activity. Experiments demonstrating that the ablation of IL-23 function through either genetic manipulation (for example, knockout mice) or pharmacology (for example, anti-IL-23 antibodies) leads to decreased tumour incidence or delayed progression, support the equivalent, inverse hypothesis that decreased IL-23 activity may protect from tumour development. The current clinical and non-clinical data do not suggest that mirikizumab causes malignant tumours or promotes tumour growth.

Evidence source(s) and strength of evidence:

Some studies have found UC (Jussila et al. 2013; Manninen et al. 2013; Hovde et al. 2017) and CD (Mizushima et al. 2010; Jess et al. 2013; Jung et al. 2017; Wu et al. 2023) to be associated with an increased risk of malignancy), which may be confounded by behavioural risk factors and current use of certain therapies to treat the disease (for example, thiopurine use).

In participants with IBD who received mirikizumab, the frequency of malignancies was low, and the data suggest there was no increase in the frequency of malignancy events with increasing duration of mirikizumab treatment. The IR (per 100 patient-years) of malignancies in this population (0.5) was consistent with the reported background IRs in the IBD population (Bernstein et al. 2001b; Jussila et al. 2013; Biancone et al. 2016; Taborelli et al. 2020; Wu et al. 2023) and did not suggest an increased risk associated with mirikizumab use.

Characterisation of the risk:

Placebo-controlled induction exposures:

UC:

In the placebo-controlled induction study, malignancies were reported in participants who received mirikizumab (0.2%).

CD:

Malignancies were not reported in the placebo-controlled induction period.

All IBD exposures:

Among participants with UC and CD in the IBD clinical development programme (N = 2632; PYE = 5884.4), 29 participants (1.1%, IR 0.5) reported ≥1 TE malignancy, which included 23 participants with malignancies excluding NMSC and 6 participants with NMSC.

All mirikizumab exposures:

Across the entire mirikizumab clinical development programme, including participants with psoriasis, UC, and CD (N=4802; total PYE=11772.8), 70 participants (1.5%, IR 0.6) reported ≥1 TE malignancy, which included 52 participants with malignancies excluding NMSC and 19 participants with NMSC.

Risk factors and risk groups:

None identified.

Preventability:

Early detection based on enhanced routine monitoring, which is common medical practice in a population at risk, has a significant impact on the progression of malignant disease, treatment success, or even prevention if pre-cancerous lesions are identified and addressed appropriately.

Impact on the risk-benefit balance of the product:

Based on the cumulative data, there is insufficient scientific evidence to suggest an association between mirikizumab and malignancy at this time. Patients with IBD are at a known increased risk for malignancy, which may be additionally confounded by individual behavioural risk factors and concurrent use of certain therapies to treat the disease.

This assessment is based on the clinical profile from the IBD clinical trial database, with exposure from 2632 patients (5884.4 PYE). In the IBD clinical development programme, malignancy has been reported in 29 participants (1.1%, IR 0.5). The IR for malignancies was consistent with the reported background IRs in the IBD population.

UC and CD have been associated with an increased risk of cancer relative to the general population (Karlén et al. 1999; Jussila et al. 2013; Jung et al. 2017; Burisch et al. 2022; Wu et al. 2023, Jess et al 2013). As such, the observed rate of malignancies seen in the mirikizumab-

treated population in the clinical development programme is considered to reflect the presence of this co-morbidity in the target population rather than a potential effect of the drug.

Lilly will monitor reported events of malignancy in the context of mirikizumab exposure through routine pharmacovigilance activities and based on the proposed additional pharmacovigilance activity on long-term safety entitled "Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab in Routine Clinical Practice Using US Administration Claims Data", of which malignancy is an objective.

Public health impact:

Given the low incidence of malignancy events in the range of disease-related background rates and that a potential risk of malignancy will only affect a small fraction of the adult population, the potential public health impact is considered negligible at this time.

Important Potential Risk 4: MACE

Potential mechanisms:

Autoimmune diseases are known to be associated with increased cardiovascular morbidity and mortality (Pujades-Rodriguez et al. 2016). Chronic and systemic inflammation, largely attributed to the presence of pro-inflammatory cytokines and auto-antibodies, is thought to underlie these observed associations. The role of IL-23 as a pro-inflammatory cytokine in vascular inflammation and atherosclerosis is not known.

Furthermore, there is no conclusive mechanism regarding CCV disease with IL-23p19 inhibition. Some authors have suggested that a risk may exist due to a therapeutically induced acute change in the immunologic environment, specifically inhibition of helper T cell sub-type 17, which may disrupt homeostasis between pro-atherogenic and protective effects. Because IL-23 plays a key role in maintaining homeostasis within the CCV system, it has been hypothesised that inhibition of IL-23 may result in pathogenic shifts which destabilise atherosclerotic plaques; however, clinical relevance of these hypotheses is uncertain.

Evidence source(s) and strength of evidence:

In the IBD population, there was no observed association between mirikizumab treatment and MACE. No cases of MACE were observed in mirikizumab-treated participants in the UC and CD placebo-controlled populations. There was a small numerical imbalance of MACE between treatment groups in the placebo-controlled psoriasis study population, with the randomisation ratio of mirikizumab to placebo of 6:1 being a contributing factor.

Incidence rates for MACE observed in the All IBD Mirikizumab Integrated Analysis Set (IR=0.2) and the All Mirikizumab Exposures Integrated Analysis Set (IR=0.3) are lower than background rates observed in the UC and CD populations (IRs=1.1 and 0.82, respectively [Kristensen et al. 2013]), and psoriasis population (IR=0.4 to 1.5; Gottlieb et al. 2014; Ogdie et al. 2015; Parisi et al. 2015; Curtis et al. 2016).

Characterisation of the risk:

Placebo-controlled induction exposures:

UC:

In the placebo-controlled induction study, adjudicated and confirmed MACEs were not reported in participants who received mirikizumab.

CD:

In the placebo-controlled induction period, adjudicated and confirmed MACEs were not reported in participants who received mirikizumab.

All IBD exposures:

In the IBD exposures in the Phase 2 and Phase 3 clinical trials for UC and CD (N=2459), adjudicated and confirmed MACEs were reported in 9 participants (0.4%, IR=0.2).

All mirikizumab exposures:

In all mirikizumab exposures in Phase 2 and Phase 3 clinical trials for UC, CD, and psoriasis (N=4593), adjudicated and confirmed MACEs were reported in 31 participants (0.7%, IR=0.3).This IR of adjudicated and confirmed MACE is below the range of the background IR in the UC and CD populations (IRs=1.1 and 0.82, respectively) and moderate-to-severe psoriasis population (0.4 to 1.5 IR) and within rates for other IL-23p19 inhibitors (IR=0.2 to 0.6; EMA 2019; Reich et al. 2019; Bissonnette et al. 2020; FDA 2017) approved for the treatment of psoriasis.

Risk factors and risk groups:

None identified.

Preventability:

Cardiovascular disorders, including CCV events, CHD, VTE, DVT, and PE, are known, important co-morbidities of the IBD population and may increase the risk of MACE. Furthermore, chronic inflammation increases the risk for MACE (Hansson 2005). Controlling inflammation through the use of mirikizumab could decrease the risk of MACE.

Impact on the risk-benefit balance of the product:

Based on the cumulative data, there is insufficient scientific evidence to suggest an association between mirikizumab and MACE. This assessment is based on the IBD clinical trial database, with exposures of 2459 patients with UC or CD (5472.6 PYE). In the IBD clinical development programme, 9 participants were confirmed after independent adjudication to have experienced a MACE, with an IR of 0.2. Patients with IBD are at a known increased risk for cardiovascular disorders. Therefore, the totality of the data, including the lack of a conclusive biological mechanism for MACE with IL-23p19 inhibition and few TE MACEs reported from all participants with IBD and psoriasis, does not represent sufficient scientific evidence of a relationship of MACE with mirikizumab treatment.

Lilly will monitor reported MACEs in the context of exposure to mirikizumab through routine pharmacovigilance activities and based on the proposed additional pharmacovigilance activity on long-term safety entitled “Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab in Routine Clinical Practice Using US Administrative Claims Data”, of which MACE is an objective.

Public health impact:
Given the low incidence of MACE in the clinical development programme of mirikizumab within the range of disease-related background rates, and the fact that a potential risk of MACE will only affect a small fraction of the adult population, the potential public health impact is considered negligible at this time.

SVII.3.2 Presentation of the Missing Information

Missing Information: Safety of mirikizumab in pregnant women and lactating women.

Evidence source:

Based on the mechanism of action, non-clinical data, and limited to no clinical trial data, the safety profile of mirikizumab is not expected to be different in pregnant women and lactating women.

Population in need of further characterisation:

Pregnant women and lactating women with moderately to severely active UC and CD.

Module SVIII - Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Serious infections • Severe liver injury • Malignancies • MACE
Missing information	• Safety of mirikizumab in pregnant women and lactating women

Abbreviation: MACE = major adverse cardiac event.

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

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Routine follow-up will be conducted on events of special interest.

Specific adverse reaction follow-up questionnaires for safety concerns:

- Spontaneous Follow-up Form – Infections – Unspecified Infection
- Spontaneous Follow-up Form – Infection – Extrapulmonary Tuberculosis
- Spontaneous Follow-up Form – Infection – Pulmonary Tuberculosis
- Spontaneous Follow-up Form – Pregnancy Data Collection – Maternal
- Spontaneous Follow-up Form – Pregnancy Data Collection – Paternal
- Spontaneous Follow-up Form – Pregnancy Outcome – Maternal
- Spontaneous Follow-up Form – Pregnancy Outcome – Paternal
- Spontaneous Follow-up Form – Breast feeding
- Spontaneous Follow-up Form – Hepatic Disorders
- Spontaneous Follow-up Form – Cancer
- Spontaneous Follow-up Form – Cardiac Disorders, and
- Spontaneous Follow-up Form – Cerebrovascular Accident

Other forms of routine pharmacovigilance activities for safety concerns:

Routine review of EudraVigilance data will be performed in conjunction with Eli Lilly and Company's routine signal evaluation processes.

III.2 Additional Pharmacovigilance Activities

Study I6T-MC-B003: Observational Study of Pregnancy and Infant Outcomes among Women Exposed to Mirikizumab during Pregnancy in US-Based Administrative Claims Data.

Rationale and Study Objectives:

Pregnant women were not included in the mirikizumab clinical development programme. However, the population of patients with UC or CD potentially exposed to mirikizumab treatment include women of childbearing age. Therefore, exposure to mirikizumab during pregnancy may occur during post-marketing use. Although there were no mirikizumab-related adverse effects on embryo-foetal development, pregnancy outcome, and peri- and post-natal development in pregnant monkeys administered mirikizumab, such potential effects in humans have not been fully determined. Therefore, the purpose of this study is to determine pregnancy, and foetal or infant outcomes among pregnant women with UC or CD who are exposed to mirikizumab.

The pregnancy, maternal and foetal or infant outcomes of interest include:

- Pregnancy outcomes: recognised spontaneous abortions, stillbirths, and preterm delivery, and
- Foetal or infant outcomes: small for gestational age, and major congenital malformations.

Study objectives:

1. To monitor the use of mirikizumab among women of childbearing age.
2. To determine the incidence of pregnancy and foetal or infant outcomes among pregnant women with a diagnosis of UC or CD who are exposed to mirikizumab during pregnancy.
3. If sufficient sample size of women exposed to mirikizumab during pregnancy and infants linked to the exposed pregnancies are identified, to compare the incidence of pregnancy and foetal or infant outcomes of pregnant women with UC or CD who are exposed to mirikizumab during pregnancy to pregnant women with UC or CD who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC or CD, respectively.

Study Design:

Observational cohort study using secondary data from administrative commercial insurance claims databases.

Study Population:

Pregnant women diagnosed with UC or CD.

Milestones:

The proposed milestones are as follows:

Milestones	**Anticipated due date**
Start of data collection*	Within 2 years of first regulatory approval
Study progress report	To be provided with the PSUR†
Interim report	Approximately 4 years after the start of data collection
Final study report	31 Dec 2031

Abbreviation: PSUR = periodic safety update report.

*Start of data collection is the date of first data extraction.

†After the start of data collection.

Study I6T-MC-B004: Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab in Routine Clinical Practice Using US Administrative Claims Data

Rationale and Study Objectives:

Data from clinical trials demonstrate that mirikizumab is effective in the treatment of patients with moderate to severe UC and CD. However, the long-term safety of mirikizumab exposure in terms of events with a low frequency and/or long latency among patients with UC or CD in routine clinical practice has not been fully characterised. The purpose of this study is to examine the long-term safety of mirikizumab exposure in terms of MACE, malignancies excluding

NMSC, serious and opportunistic infections, and severe liver injury among patients with UC or CD in routine clinical practice in the US.

Study Objectives

The objective of this study is to examine the incidence of severe acute liver injury, serious infections, including opportunistic infections, malignancies excluding non-melanoma skin cancer (NMSC) and MACE among patients with a diagnosis of UC or CD who are exposed to mirikizumab compared to patients with a diagnosis of UC or CD who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC or CD, respectively, in real-world clinical practice in the US. The incidence of the study outcomes will also be examined among subgroups of interest including elderly patients 65 years of age and older.

Study Design:

Observational cohort study using secondary data from administrative commercial insurance claims databases.

Study Population:

Adult patients diagnosed with UC or CD.

Milestones:

The proposed milestones are as follows:

Milestones	**Anticipated due date**
Start of data collection*	Within 2 years of first regulatory approval
Study progress report	To be provided with the PSUR†
Interim report	Approximately 7 years after the start of data collection
Final study report	31 Dec 2037

Abbreviation: PSUR = periodic safety update report.

*Start of data collection is the date of first data extraction.

†After the start of data collection.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
I6T-MC-B003: Observational Study of Pregnancy and Infant Outcomes among Women Exposed to Mirikizumab during Pregnancy in US-Based Administrative Claims Data Planned	• To monitor the use of mirikizumab among women of childbearing age. • To determine the incidence of pregnancy- and foetal/infant outcomes among pregnant women with UC or CD who are exposed to mirikizumab during pregnancy. • If sufficient sample size allows, to compare the incidence of pregnancy and foetal/infant outcomes of women with UC or CD who are exposed to mirikizumab during pregnancy to women with UC or CD who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC or CD during pregnancy.	Missing information: Safety of mirikizumab in pregnant women	Start of data collection* Study progress report Interim report	Within 2 years of first regulatory approval To be submitted with the PSUR (after the start of data collection) Approximately 4 years after start of data collection
			Final report	31 Dec 2031

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
I6T-MC-B004: Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab in Routine Clinical Practice Using US Administrative Claims Data Planned	• The objective of this study is to examine the incidence of severe acute liver injury, serious infections including opportunistic infections, malignancies excluding non-melanoma skin cancer and MACE among patients with a diagnosis of UC or CD who are exposed to mirikizumab compared to patients with a diagnosis of UC or CD who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC or CD, respectively, in real world clinical practice in the US. The incidence of the study outcomes will also be examined among subgroups of interest including elderly patients 65 years of age and older.	Important potential risks: Severe liver injury, serious infections, malignancy, and MACE.	Start of data collection* Study progress report Interim report	Within 2 years of first regulatory approval To be submitted with the PSUR (after the start of data collection) Approximately 7 years after the start of data collection
			Final report	31 Dec 2037

Abbreviations: CD = Crohn's disease; MACE = major adverse cardiovascular event; NMSC = non-melanoma skin cancer; PSUR = periodic safety update report; UC = ulcerative colitis; US = United States.

*Start of data collection is the date of first data extraction.

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 Part V.1. Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Serious infections	Routine risk communication: • SmPC Section 4.3 • SmPC Section 4.4 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.3 contains a contraindication for the use of mirikizumab in patients with: • clinically important active infections (active TB). SmPC Section 4.4 advises: • Mirikizumab may increase the risk of severe infection (see Section 4.8). Treatment with mirikizumab should not be initiated in patients with a clinically important active infection until the infection resolves or is adequately treated. The risks and benefits of treatment should be considered prior to initiating use of mirikizumab in patients with a chronic infection or a history of recurrent infection. Patients should be instructed to seek medical advice if signs or symptoms of clinically important acute or chronic infection occur. If a serious infection develops, discontinuation of mirikizumab should be considered until the infection resolves. Pre-treatment evaluation for tuberculosis • Prior to initiating treatment, patients should be evaluated for TB infection. Patients receiving mirikizumab should be monitored for signs and symptoms of active TB during and after treatment. Anti-TB therapy should be considered prior to initiating treatment in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. PL Section 2 advises: Do not use mirikizumab if you have important active infections (active TB). • Mirikizumab can potentially cause serious infections. • Treatment with mirikizumab should not be started if you have an active infection until the infection is gone. • After starting the treatment, tell your doctor right away if you have any symptoms of an infection such as o fever o chills o muscle aches o cough o shortness of breath

Safety concern	Routine risk minimisation activities
	○ runny nose ○ sore throat ○ pain during urination • Also tell your doctor if you have recently been near anyone who might have TB. • Your doctor will examine you and may do a test for TB, before you have mirikizumab. • If your doctor thinks you are at risk of an active TB, you may be given medicines to treat it. Pack size: Not applicable Legal status: Not applicable
Severe Liver Injury	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 advises: • Cases of drug-induced liver injury (including one case meeting Hy's Law criteria) occurred in patients receiving mirikizumab in clinical trials. • Liver enzymes and bilirubin should be evaluated at baseline and monthly during induction (including extended induction period, if applicable). Thereafter, liver enzymes and bilirubin should be monitored (every 1-4 months) according to standard practice for patient management and as clinically indicated. If increases in ALT or AST are observed and drug-induced liver injury is suspected, mirikizumab must be discontinued until this diagnosis is excluded. SmPC Section 4.8 indicates: • Overall mirikizumab treatment periods in the ulcerative colitis and Crohn's disease clinical development programme (including the placebo-controlled and open-label induction and maintenance periods), there have been elevations of ALT to ≥3× upper limit of normal (ULN) (2.3%), ≥5×ULN (0.7%) and ≥10×ULN (0.1%) and AST to ≥3×ULN (2.2%), ≥5×ULN (0.8%), and ≥10×ULN (0.1%) in patients receiving mirikizumab (see Section 4.4). These elevations have been noted with and without concomitant elevations in total bilirubin. PL Section 2 advises • Your doctor will conduct blood tests before starting and during treatment with mirikizumab to check if your liver is functioning normally. If blood tests are abnormal, your doctor might interrupt therapy with mirikizumab and do additional tests on your liver to determine the cause. Pack size: Not applicable Legal status: Not applicable
Malignancies	Routine risk communication: None
MACE	Routine risk communication: None

Safety concern	Routine risk minimisation activities
Safety of mirikizumab in pregnant women and lactating women	Routine risk communication: • SmPC Section 4.6 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.6 provides guidance: • Women of childbearing potential should use an effective method of contraception during treatment and for at least 10 weeks after treatment. • There is a limited amount of data from the use of mirikizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see Section 5.3). As a precautionary measure, it is preferable to avoid the use of mirikizumab during pregnancy. • It is unknown whether mirikizumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Omvoh therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. PL Section 2 advises: • If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before using this medicine. It is preferable to avoid the use of mirikizumab in pregnancy. The effects of mirikizumab in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and should use adequate contraception while using mirikizumab and for at least 10 weeks after the last mirikizumab dose. • If you are breast feeding or are planning to breast-feed, talk to your doctor before using this medicine. Pack size: Not applicable. Legal status: Not applicable.

Abbreviation: ALT = alanine aminotransferase; AST = aspartate aminotransferase; MACE = major adverse cardiac event; PL = package leaflet; SmPC = summary of product characteristics; TB = tuberculosis; ULN = upper limit of normal.

V.2 Additional Risk Minimisation Measures

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

V.3 Summary of Risk Minimisation Measures

Table Part V.3. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Serious infections	Routine risk minimisation measures: • SmPC Section 4.3 Contraindications • SmPC Section 4.4 Special Warnings and Precautions for Use • PL Section 2 Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection include the following: • Spontaneous Follow-up Form - Infections – Unspecified Infection • Spontaneous Follow-up Form - Infections – Extrapulmonary Tuberculosis • Spontaneous Follow-up Form - Infections – Pulmonary Tuberculosis Additional pharmacovigilance activities: I6T-MC-B004: An Observational Secondary Database Study to Assess the Long-term Safety of Mirikizumab in Routine Clinical Practice Using US Administrative Claims Data. • To examine the incidence of severe acute liver injury, **serious infections including opportunistic infections**, malignancies excluding non-melanoma skin cancer (NMSC), and MACE among patients with a diagnosis of UC or CD who are exposed to mirikizumab compared to patients with a diagnosis of UC or CD who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC or CD, respectively, in real world clinical practice in the US. The incidence of the study outcomes will also be examined among subgroups of interest, including elderly patients 65 years of age and older.
Severe liver injury	Routine risk minimisation measures: • SmPC Section 4.4 Special Warnings and Precautions for Use • SmPC Section 4.8 Undesirable Effects • PL Section 2 Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection include the following: Spontaneous Follow-up Form - Hepatic Disorders Additional pharmacovigilance activities: I6T-MC-B004: An Observational Secondary Database Study to Assess the Long-term Safety of Mirikizumab in Routine Clinical

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		Practice Using US Administrative Claims Data. • To examine the incidence of **severe acute liver injury**, serious infections including opportunistic infections, malignancies excluding non-melanoma skin cancer (NMSC), and MACE among patients with a diagnosis of UC or CD who are exposed to mirikizumab compared to patients with a diagnosis of UC or CD who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC or CD, respectively, in real world clinical practice in the US. The incidence of the study outcomes will also be examined among subgroups of interest, including elderly patients 65 years of age and older.
Malignancies	Routine risk minimisation measures: None Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection include the following: • Spontaneous Follow-up Form - Cancer Additional pharmacovigilance activities: I6T-MC-B004: An Observational Secondary Database Study to Assess the Long-term Safety of Mirikizumab in Routine Clinical Practice Using US Administrative Claims Data. • To examine the incidence of severe acute liver injury, serious infections including opportunistic infections, **malignancies excluding non-melanoma skin cancer (NMSC)**, and MACE among patients with a diagnosis of UC or CD who are exposed to mirikizumab compared to patients with a diagnosis of UC or CD who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC or CD, respectively, in real world clinical practice in the US. The incidence of the study outcomes will also be examined among subgroups of interest, including elderly patients 65 years of age and older.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
MACE	Routine risk minimisation measures: None Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection include the following: • Spontaneous Follow-up Form – Cardiac Disorders • Spontaneous Follow-up Form - Cerebrovascular Accident Additional pharmacovigilance activities: I6T-MC-B004: An Observational Secondary Database Study to Assess the Long-term Safety of Mirikizumab in Routine Clinical Practice Using US Administrative Claims Data. To examine the incidence of severe acute liver injury, serious infections including opportunistic infections, malignancies excluding non-melanoma skin cancer (NMSC), and **MACE** among patients with a diagnosis of UC or CD who are exposed to mirikizumab compared to patients with a diagnosis of UC or CD who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC or CD, respectively, in real world clinical practice in the US. The incidence of the study outcomes will also be examined among subgroups of interest, including elderly patients 65 years of age and older.
Safety of mirikizumab in pregnant women and lactating women	Routine risk minimisation measures: • SmPC Section 4.6 Fertility, Pregnancy, and Lactation • PL Section 2 Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection include the following: • Spontaneous Follow-up Form – Pregnancy Data Collection – Maternal • Spontaneous Follow-Up Form – Pregnancy Data Collection – Paternal • Spontaneous Follow-Up Form – Pregnancy Outcome – Maternal • Spontaneous Follow-Up Form – Pregnancy Outcome – Paternal • Spontaneous Follow-Up Form – Breast Feeding Additional pharmacovigilance activities: I6T-MC-B003: Observational Study of **Pregnancy and Infant Outcomes** among Women Exposed to Mirikizumab during

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		Pregnancy in US-Based Administrative Claims Data: • To monitor the use of mirikizumab among women of childbearing age. • To determine the incidence of **pregnancy and foetal or infant outcomes** among pregnant women with UC or CD who are exposed to mirikizumab during pregnancy. • If sufficient sample sizes allow to compare the incidence of **pregnancy and foetal/infant outcomes** of pregnant women with UC or CD who are exposed to mirikizumab during pregnancy to women with UC or CD who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC or CD.

Abbreviations: CD = Crohn's disease; MACE = major adverse cardiac event; NMSC = non-melanoma skin cancer; PL = package leaflet; SmPC = summary of product characteristics; UC = ulcerative colitis; US = United States.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Mirikizumab (LY3074828)

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

Mirikizumab's SmPC and its package leaflet give essential information to health care professionals and patients on how mirikizumab should be used.

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

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

I - The Medicine and What It is Used for

Mirikizumab is indicated for UC (see SmPC for the full indication). Mirikizumab is the active substance, and it is given by IV infusion (after dilution) and by subcutaneous injection.

Further information about the evaluation of mirikizumab's benefits can be found in mirikizumab's European Public Assessment Report, including in it's plain-language summary, available on the European Medicines Agency website, under the medicine's webpage.

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

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

Measure 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 health care professionals.

This constitutes *routine risk minimisation* measure.

In addition to this measure, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. This measure constitutes *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of mirikizumab 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 mirikizumab. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this

association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	• Serious infections • Severe liver injury • Malignancies • MACE
Missing information	• Safety of mirikizumab in pregnant women and lactating women

Abbreviation: MACE = major adverse cardiac event.

II.B Summary of Important Risks

Important potential risk: Serious infections	
Evidence for linking the risk to the medicine	In participants with IBD across the Phase 2 and Phase 3 studies for UC and CD, serious infections (n=76, 2.9%, EAIR 1.4) were reported commonly during treatment with mirikizumab. When including time off mirikizumab (defined as the time from mirikizumab discontinuation to either study discontinuation or, in the case of the Phase 3 UC maintenance study, the resumption of mirikizumab in mirikizumab responders who were re-randomised to placebo), serious infections (n=82, 3.1%, EAIR 1.4) were also reported commonly. Although the majority of participants with IBD who reported serious infections recovered, recovered with sequelae, or were recovering, serious infections resulted in the death of 6 participants with IBD. Across all mirikizumab exposures in Phase 2 and Phase 3 clinical trials for UC, CD, and psoriasis, serious infections (n=142, 3.0%, EAIR 1.3) have been reported commonly during treatment with mirikizumab. Although the majority of patients recovered, serious infections due to COVID-19 or coronavirus infections or sequelae of COVID-19 infection resulted in the deaths of 9 patients. Eight of the 9 deaths due to coronavirus or COVID-19 infection or sequelae of COVID-19 infection in the mirikizumab programme occurred early in the COVID-19 pandemic, prior to the availability of effective treatments and vaccinations. Furthermore, these patients with fatal COVID-19 infections were at increased risk for hospitalisation, severe disease, and/or death due to COVID-19 based on one or more of the following criteria: age ≥65 years, smoking, obesity, diabetes mellitus, cardiovascular disease, hypertension, liver disease, and/or malignancy. None of these deaths from severe COVID-19/coronavirus infection or sequelae of COVID-19 infection were determined by the investigator or sponsor to be related to mirikizumab.
Risk factors and risk groups	Risk groups or specific risk factors for serious infections have not been identified from the clinical development programme. Due to the immunomodulatory effect of medicines in the anti-IL23 class, patients with evidence of untreated latent TB or other active, chronic, or recurrent infections or a history thereof may be at greater risk of reactivation or

	exacerbation of their underlying infection, even though this has not been reported in the mirikizumab clinical development programme.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.3, Contraindications • SmPC Section 4.4, Special Warnings and Precautions for Use • PL Section 2 Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	Additional pharmacovigilance activities: I6T-MC-B004: An Observational Secondary Database Study to Assess the Long-term Safety of Mirikizumab in Routine Clinical Practice Using US Administrative Claims Data. See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Severe Liver Injury	
Evidence for linking the risk to the medicine	For all mirikizumab exposures in Phase 2 and Phase 3 clinical trials for UC, CD, and psoriasis, elevated ALT and AST ≥10×ULN was reported for each analyte in 0.2% of mirikizumab-treated participants. Most of these liver enzyme elevations/increases were considered mild to moderate in severity, and 3 patients with psoriasis had AST and or ALT elevations that were reported as serious. None were associated with an adverse clinical outcome. Overall, 0.3% of participants discontinued due to a TEAE of liver enzyme elevation. Most recovered from the liver enzyme elevations while continuing on mirikizumab treatment and with no further adverse effects. One mirikizumab treatment participant with UC met Hy's law criteria with a maximum ALT of 17.9×ULN, maximum AST of 9.9×ULN, and maximum bilirubin of 2.4×ULN. This TEAE of "hepatic enzyme increased" was reported as moderate severity and as non-serious. Upon discontinuation of mirikizumab, hepatic enzymes rapidly resolved. As no alternative aetiology for the liver function test elevations could be determined, an association with mirikizumab treatment could not be excluded. Therefore, based on the potential of significantly elevated aminotransferases being indicative of possible severe liver injury, it is considered an important potential risk.
Risk factors and risk groups	In the UC, CD, and psoriasis programmes, no specific risk groups or specific risk factors have been identified, although concurrent use of alcohol and/or medications with a known risk of liver enzyme elevation or DILI may result in a higher frequency of liver enzyme elevations and possible liver injury. Additionally, clinical observations of transient elevations of liver enzymes with no known cause and persistent elevations most commonly due to PSC, AIH, cholelithiasis, and NAFLD, and some herbal, dietary, and traditional healing and supplemental products may also contribute to a higher frequency of liver enzyme elevations and possible liver injury. In the IBD clinical development programme, no specific risk factors have been identified.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4, Special Warnings and Precautions for Use

	• SmPC Section 4.8, Undesirable Effects • PL Section 2 Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	Additional pharmacovigilance activities: I6T-MC-B004: An Observational Secondary Database Study to Assess the Long-term Safety of Mirikizumab in Routine Clinical Practice Using US Administrative Claims Data. See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Malignancies	
Evidence for linking the risk to the medicine	There are theoretical considerations which could link the pharmacologic mode of action of mirikizumab to the development of tumours; however, the current clinical and non-clinical data do not suggest that mirikizumab causes malignant tumours or promotes tumour growth.
Risk factors and risk groups	No specific risk factors for malignancy in relation to treatment with mirikizumab have been identified.
Risk minimisation measures	None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: I6T-MC-B004: An Observational Secondary Database Study to Assess the Long-term Safety of Mirikizumab in Routine Clinical Practice Using US Administrative Claims Data. See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: MACE	
Evidence for linking the risk to the medicine	There is no conclusive mechanism of action for cerebrocardiovascular disease with IL-23p19 inhibition. A risk may exist due to a therapeutically induced acute change in the immunologic environment, specifically inhibition of helper T cell sub-type 17, which may disrupt homeostasis between pro-atherogenic and protective effects. Because IL-23 plays a key role in maintaining homeostasis within the cerebrocardiovascular (CCV) system, it has been hypothesised that inhibition of IL-23 may result in pathogenic shifts which destabilise atherosclerotic plaques; however, clinical relevance of these hypotheses are uncertain.
Risk factors and risk groups	No specific risk factors for MACE in relation to treatment with mirikizumab have been identified.
Risk minimisation measures	None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: I6T-MC-B004: An Observational Secondary Database Study to Assess the Long-term Safety of Mirikizumab in Routine Clinical Practice Using US Administrative Claims Data. See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviation: AIH = autoimmune hepatitis; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CD = Crohn's disease; COVID-19 = coronavirus disease 2019; DILI = drug-induced liver injury; IL = interleukin; LFT = liver function test; MACE = major adverse cardiovascular event; n = number of patients in the specified category; NAFLD = non-alcoholic fatty liver disease; PSC = primary sclerosing cholangitis; SmPC = summary of product characteristics; TB = tuberculosis; TEAE = treatment-emergent adverse event; UC = ulcerative colitis; ULN = upper limit of normal.

Missing information: Safety of mirikizumab in pregnant women and lactating women	
Risk minimisation measures	Routine risk minimisation measures • SmPC Section 4.6, Fertility, Pregnancy, and Lactation • PL Section 2 Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	Additional pharmacovigilance activities: I6T-MC-B003: Observational Study of Pregnancy and Infant Outcomes among Women Exposed to Mirikizumab during Pregnancy in US-Based Administrative Claims Data See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: PL = package leaflet; SmPC = summary of product characteristics.

II.C Post-Authorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of mirikizumab.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study I6T-MC-B003: Observational Study of Pregnancy and Infant Outcomes among Women Exposed to Mirikizumab during Pregnancy in US-Based Administrative Claims Data.

Purpose of the study: Pregnant women were not included in the mirikizumab clinical development programme. However, the population of patients with UC or CD potentially exposed to mirikizumab treatment include women of childbearing age. Therefore, exposure to mirikizumab during pregnancy may occur during post-marketing use. Although there were no mirikizumab-related adverse effects on embryo-foetal development, pregnancy outcome, and peri- and post-natal development in pregnant monkeys administered mirikizumab, such potential effects in humans have not been fully determined. Therefore, the purpose of this study is to determine pregnancy, and foetal or infant outcomes among pregnant women with UC or CD who are exposed to mirikizumab.

The pregnancy, maternal and foetal or infant outcomes of interest include:

1. Pregnancy outcomes: recognised spontaneous abortions, stillbirths, and preterm delivery, and
2. Foetal or infant outcomes: small for gestational age, and major congenital malformations.

Study objectives:

1. To monitor the use of mirikizumab among women of childbearing age.
2. To determine the incidence of pregnancy and foetal or infant outcomes among pregnant women with a diagnosis of UC or CD who are exposed to mirikizumab during pregnancy.
3. If sufficient sample size of women exposed to mirikizumab during pregnancy and infants linked to the exposed pregnancies are identified, to compare the incidence of pregnancy

and foetal or infant outcomes of pregnant women with UC or CD who are exposed to mirikizumab during pregnancy to pregnant women with UC or CD who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC or CD, respectively.

Study I6T-MC-B004: Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab in Routine Clinical Practice Using US Administrative Claims Data

Purpose of the study: Data from clinical trials demonstrate that mirikizumab is effective in the treatment of patients with moderate to severe UC and CD. However, the long-term safety of mirikizumab exposure in terms of events with a low frequency and/or long latency among patients with UC or CD in routine clinical practice has not been fully characterised. The purpose of this study is to examine the long-term safety of mirikizumab exposure in terms of MACE, malignancies excluding NMSC, serious and opportunistic infections, and severe liver injury among patients with UC or CD in routine clinical practice in the US.

Study Objectives

The objective of this study is to examine the incidence of severe acute liver injury, serious infections, including opportunistic infections, malignancies excluding non-melanoma skin cancer (NMSC) and MACE among patients with a diagnosis of UC or CD who are exposed to mirikizumab compared to patients with a diagnosis of UC or CD who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC or CD, respectively, in real-world clinical practice in the US. The incidence of the study outcomes will also be examined among subgroups of interest including elderly patients 65 years of age and older.

Part VII: Annexes

Annex **Page**

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Follow-up forms

Specific Adverse Event Follow-up Form	Event(s) Associated with the Form
Form #1	Infections – Unspecified Infection
Form #2	Infections – Extrapulmonary Tuberculosis
Form #3	Infections – Pulmonary Tuberculosis
Form #4	Pregnancy Data Collection - Maternal
Form #5	Pregnancy Data Collection - Paternal
Form #6	Pregnancy Outcome - Maternal
Form #7	Pregnancy Outcome - Paternal
Form #8	Breast feeding
Form #9	Hepatic Disorders
Form #10	Cancer
Form #11	Cardiac Disorders
Form #12	Cerebrovascular Accident

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender:	Race:	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Unspecified Infection	
General	
Type of Infection:	
Presenting Signs and Symptoms:	
Relevant Medical History and Risk Factors:	
Relevant Diagnostic Studies	
Cultures:	
Antigen Detection:	
Serologic Studies:	
Imaging Studies:	
Tissue Biopsy:	

Laboratory Results:				
Laboratory Test	**Normal Range**	**Baseline Value**	**Abnormal Value**	**Improvement Value**
		Date:	Date:	Date:
Neutrophils				
Haemoglobin				
WBC				
Platelets				
ALT				
AST				
Alkaline Phosphatase				
Bilirubin				
Creatinine				
Other:				

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender: ☐ M ☐ F ☐ Unknown	Race: ☐ Caucasian ☐ Asian ☐ Black ☐ Other	Weight: ☐ lb ☐ kg	Height: ☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Extrapulmonary Tuberculosis			
Site(s) of Infection:			
Presenting Symptoms			
☐ Cough	☐ Fever	☐ Headache	☐ Joint swelling
☐ Sputum	☐ Night sweats	☐ Confusion	☐ Skin lesions
☐ Weight loss	☐ Haemoptysis	☐ Back pain	☐ Lymphadenopathy
☐ Focal neurological findings	☐ Pyuria	☐ Nuchal rigidity	☐ Anaemia
Relevant Past Medical History			
☐ Tuberculosis	☐ Abnormal chest X-ray	☐ Smoking	☐ Corticosteroid use
☐ Positive PPD	☐ Diabetes mellitus	☐ Family member with TB	☐ Heavy alcohol use
☐ Positive IFN-y release assay	☐ From TB endemic area	☐ BCG immunization	☐ Treatment with INH
☐ HIV infection	☐ Autoimmune disorder	☐ Malignancy	☐ Cancer chemo Rx
☐ Other Relevant History:			
Concomitant Medications/Substances			
☐ Current alcohol use	☐ Current smoking	☐ Drug abuse	
☐ Corticosteroids (specify):			
☐ Immunomodulators (specify):			
☐ Other medications:			

Laboratory Tests/Investigations				
Skin test for TB	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
IFN-y release assay	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Sputum smear for TB	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Sputum culture for TB	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Antigen detection	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
HIV serology	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
CSF cultures	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Urine cultures	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Bone marrow cultures	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Other cultures (site)	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Chest radiograph:				
Chest CT:				
Other studies:				

Eli Lilly and Company - Global Patient Safety **Case Number:**

Laboratory Results

Laboratory Test	Normal Range	Baseline Value	Abnormal Value	Improvement Value
		Date:	Date:	Date:
Neutrophils				
Haemoglobin				
WBC				
Platelets				
ALT				
AST				
Alkaline Phosphatase				
Bilirubin				
Creatinine				
CSF Cell Count				
CSF Glucose				
Urinalysis				
Other:				

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown

Event outcome:
☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown
☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender:	Race:	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Pulmonary Tuberculosis			
Presenting Symptoms			
☐ Cough	☐ Fever	☐ Headache	☐ Joint swelling
☐ Sputum	☐ Night sweats	☐ Confusion	☐ Skin lesions
☐ Weight loss	☐ Haemoptysis	☐ Back pain	☐ Lymphadenopathy
Relevant Past Medical History			
☐ Tuberculosis	☐ Abnormal Chest X-ray	☐ Smoking	☐ Corticosteroid Use
☐ Positive PPD	☐ Diabetes Mellitus	☐ Family Member with TB	☐ Heavy Alcohol Use
☐ Positive IFN-y Release Assay	☐ From TB Endemic Area	☐ BCG Immunization	☐ Treatment with INH
☐ HIV Infection	☐ Autoimmune Disorder	☐ Malignancy	☐ Cancer Chemo Rx
☐ Other Relevant History:			
Concomitant Medications / Substances			
☐ Current Alcohol Use	☐ Current Smoking	☐ Drug Abuse	
☐ Corticosteroids (specify):			
☐ Immunomodulators (specify):			
☐ Other Medications:			

Laboratory Tests / Investigations				
Skin Test for TB	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
IFN-y Release Assay	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Sputum Smear for TB	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Sputum Culture for TB	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Antigen Detection	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
HIV Serology	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Chest Radiograph:				
Chest CT:				
Other Studies:				

Laboratory Results:				
Laboratory Test	**Normal Range**	**Baseline Value**	**Abnormal Value**	**Improvement Value**
		Date:	Date:	Date:
Neutrophils				
Haemoglobin				
WBC				
Platelets				

Eli Lilly and Company - Global Patient Safety **Case Number:**

ALT				
AST				
Alkaline Phosphatase				
Bilirubin				
Creatinine				
Other:				

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown

Event outcome:
☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown
☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Pregnancy Data Collection – Maternal	
Pregnancy Details	
Name or initials:	Date of Birth or Age:
Due Date:	Last menstrual period:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)					
Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	☐ M ☐ F				

Maternal medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)

Contraceptive method:

Exposure Period for Lilly Drug Used During Current Pregnancy

Exposure period - Weeks gestation:
☐ 0-12 weeks/1st trimester ☐ 13-24 weeks/2nd trimester ☐ 25 plus weeks/3rd trimester

Maternal Concomitant Medications/Substance (please include prescription, OTC, and herbal)

Maternal Complications

Has the mother experienced any complications during this pregnancy? ☐ No ☐ Yes

Define complications:

Treatment:

Continuing: ☐ No ☐ Yes

Maternal Testing Performed (such as, amniocentesis, ultrasound, and so forth.)

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown

Event outcome:
☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown
☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Additional Contact Information	
Medical professional responsible for monitoring patient's pregnancy:	Medical professional responsible for monitoring the infant:
Name:	Name:
Address:	Address:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Phone:	Phone:
Fax:	Fax:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Pregnancy Data Collection – Paternal

Patient (Father) Details

Name or initials:	Date of Birth or Age:

Father's medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)

Pregnancy Details

Name or initials:	Date of Birth or Age:
Due Date:	Last menstrual period:

Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)

Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	☐ M ☐ F				

Maternal medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)

Contraceptive method:

Exposure Period for Lilly Drug Used During Current Pregnancy

Exposure period - Weeks gestation:
☐ 0-12 weeks/1st trimester ☐ 13-24 weeks/2nd trimester ☐ 25 plus weeks/3rd trimester

Paternal Concomitant Medications/Substance (please include prescription, OTC, and herbal)

Maternal Complications

Has the mother experienced any complications during this pregnancy? ☐ No ☐ Yes

Define complications:

Treatment:

Continuing: ☐ No ☐ Yes

Maternal Testing Performed (such as, amniocentesis, ultrasound, and so forth.)

Eli Lilly and Company - Global Patient Safety **Case Number:**

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Additional Contact Information	
Medical professional responsible for monitoring the father:	Medical professional responsible for monitoring the mother:
Name:	Name:
Address:	Address:
Phone:	Phone:
Fax:	Fax:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Pregnancy Outcome Maternal

Pregnancy Details

Name or initials:	Date of Birth or Age:
Due Date:	Last menstrual period:

Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)

Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	☐ M ☐ F				

Maternal medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)

Contraceptive method:

Exposure Period for Lilly Drug Used During Current Pregnancy

Exposure period - Weeks gestation:
☐ 0-12 weeks/1st trimester ☐ 13-24 weeks/2nd trimester ☐ 25 plus weeks/3rd trimester

Maternal Concomitant Medications/Substance (please include prescription, OTC and herbal)

Maternal Complications

Has the mother experienced any complications during this pregnancy? ☐ No ☐ Yes

Define complications:

Treatment:

Continuing: ☐ No ☐ Yes

Maternal Testing Performed (such as, amniocentesis, ultrasound, and so forth.)

Breast Feeding Information

Date the breast feeding started Date the breast feeding stopped

Breast feeding continued ? ☐ No ☐ Yes

Was the breast-feeding experience 3 months or longer while on Lilly drug ☐ No ☐ Yes

Eli Lilly and Company - Global Patient Safety **Case Number:**

Pregnancy/Fetal Outcome	
☐ Live birth/full term	☐ Premature birth (less than 37 weeks)
☐ Spontaneous/missed abortion	☐ Fetal death in utero/stillbirth
☐ Live birth with neonatal death	☐ Post natal death
☐ Elective termination (provide below the reason and the gestational age at termination):	
Were congenital or chromosomal abnormalities detected? ☐ No ☐ Yes Please define:	
Did the infant experience perinatal or post-perinatal complications? ☐ No ☐ Yes Please define:	
Was the infant admitted to the neonatal intensive care unit (NICU) at birth? ☐ No ☐ Yes Please define:	
Did the infant experience an increased incidence or severity of infection? ☐ No ☐ Yes Please define:	

Neonatal/Infant Data		
Infant name or initials:	EDC (Due Date):	Date of Delivery:
Gestational age:	Gender: ☐ Undetermined/unknown ☐ Male ☐ Female	
Apgar scores: at 1 minute at 5 minutes		
Weight: ☐ grams ☐ pounds		Length: ☐ cm ☐ inches
Infant's overall health status?		

Infant Adverse Events/Complications
Did the infant experience any problems while breast feeding? ☐ No ☐ Yes
Please describe:
Treatment:
Continuing? ☐ No ☐ Yes
Infant's overall health status:

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown	

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Additional Contact Information	
Medical professional responsible for monitoring patient's pregnancy:	Medical professional responsible for monitoring the infant:
Name:	Name:
Address:	Address:
Phone:	Phone:
Fax:	Fax:

Eli Lilly and Company - Global Patient Safety **Case Number**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number**

Pregnancy Outcome Paternal

Patient (Father) Details

Name or initials:	Date of Birth or Age:

Father's medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)

Pregnancy Details

Name or initials:	Date of Birth or Age:
Due Date:	Last menstrual period:

Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)

Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	☐ M ☐ F				

Maternal medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)

Contraceptive method:

Exposure Period for Lilly Drug Used During Current Pregnancy

Exposure period - Weeks gestation:
☐ 0-12 weeks/1st trimester ☐ 13-24 weeks/2nd trimester ☐ 25 plus weeks/3rd trimester

Paternal Concomitant Medications/Substance (please include prescription, OTC, and herbal)

Maternal Complications

Has the mother experienced any complications during this pregnancy? ☐ No ☐ Yes

Define complications:

Treatment:

Continuing: ☐ No ☐ Yes

Maternal Testing Performed (such as, amniocentesis, ultrasound, and so forth.)

Eli Lilly and Company - Global Patient Safety **Case Number**

Pregnancy/Fetal Outcome	
☐ Live birth/full term	☐ Premature birth (less than 37 weeks)
☐ Spontaneous/missed abortion	☐ Fetal death in utero/stillbirth
☐ Live birth with neonatal death	☐ Post natal death
☐ Elective termination (provide below the reason and the gestational age at termination):	
Were congenital or chromosomal abnormalities detected? ☐ No ☐ Yes Please define:	
Did the infant experience perinatal or post-perinatal complications? ☐ No ☐ Yes Please define:	
Was the infant admitted to the neonatal intensive care unit (NICU) at birth? ☐ No ☐ Yes Please define:	
Did the infant experience an increased incidence or severity of infection? ☐ No ☐ Yes Please define:	

Neonatal/Infant Data		
Infant name or initials:	EDC (Due Date):	Date of Delivery:
Gestational age:	Gender: ☐ Undetermined/unknown ☐ Male ☐ Female	
Apgar scores: at 1 minute at 5 minutes		
Weight: ☐ grams ☐ pounds	Length: ☐ cm ☐ inches	
Infant's overall health status?		

Infant Adverse Events/Complications
Did the infant experience any problems while breast feeding? ☐ No ☐ Yes
Please describe:
Treatment:
Continuing? ☐ No ☐ Yes
Infant's overall health status:

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome:	

Eli Lilly and Company - Global Patient Safety **Case Number**

☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown
☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Additional Contact Information	
Medical professional responsible for monitoring the father:	Medical professional responsible for monitoring the mother:
Name:	Name:
Address:	Address:
Phone:	Phone:
Fax:	Fax:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

⊞

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Breast Feeding	
Pregnancy Details	
Name or initials:	Date of Birth or Age:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Due Date:			Last menstrual period:		
Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)					
Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	☐ M ☐ F				
Maternal medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)					
Contraceptive method:					
Maternal Lilly Drug Information					
Drug name:					
Infant's age at first use:			Date of first use:		
Infant's age at last use:			Date of last use:		
Maternal Concomitant Medications/Substance (please include prescription, OTC, and herbal)					
Breast Feeding Information					
Date the breast feeding started:			Date the breast feeding stopped:		
Breast feeding continued? ☐ No ☐ Yes					
Was the breast feeding experience 3 months or longer while on Lilly drug? ☐ No ☐ Yes					
Infant Adverse Events/Complications					
Did the infant experience any problems while breast feeding? ☐ No ☐ Yes Please describe:					
Treatment:					
Continuing? ☐ No ☐ Yes					
Infant's overall health status:					

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Additional Contact Information	
Medical professional responsible for monitoring the mother:	Medical professional responsible for monitoring the infant:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Name:	Name:
Address:	Address:
Phone:	Phone:
Fax:	Fax:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender: ☐ M ☐ F ☐ Unknown	Race: ☐ Caucasian ☐ Asian ☐ Black ☐ Other	Weight: ☐ lb ☐ kg	Height: ☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Hepatic Disorders
Start date of Event:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Primary Diagnosis for the Reported Event(s):
Has a Hepatologist/ Gastroenterologist been consulted? ☐ No ☐ Yes What were the results?
Hospitalization for this event? ☐ No ☐ Yes
Did the event result in a liver transplant? ☐ No ☐ Yes If yes, please provide the dates and details.

Presenting Signs/Symptoms		
☐ Fever	☐ Jaundice	☐ Abdominal Pain
☐ Rash	☐ Edema	☐ Ascites
☐ Joint Effusions	☐ Nausea	☐ Palmar Erythema
☐ Urticaria	☐ Confusion	☐ Asterixis
☐ Arthralgias	☐ Other (please specify):	
Concurrent Events and Disease(s)		
☐ Sepsis	☐ Kidney Failure	☐ Bleeding
☐ Hypotension	☐ Heart Failure	☐ Diabetes
☐ HIV	☐ Cor pulmonale	☐ Malignancy
☐ Tuberculosis	☐ Autoimmune disease	☐ Inflammatory bowel disease
☐ Other (please specify):		
Relevant Past Medical History		
☐ None	☐ Liver Toxin Exposure	☐ Budd-Chiari syndrome
☐ Hepatitis A	☐ Cirrhosis Child Pugh B or C	☐ Hepatic encephalopathy
☐ Hepatitis B	☐ Alcoholic liver disease	☐ Ascites
☐ Hepatitis C	☐ Autoimmune hepatitis	☐ Hepatorenal syndrome
☐ Gall bladder disease	☐ Hyperbilirubinemia/Jaundice	☐ Portal Hypertension
☐ Fatty liver	☐ Abnormal liver laboratory results	☐ Other:

Concomitant Medical Products (include prescription, OTC, and herbal)

Product Name	Dosage	Indication for Use	Therapy Start Date	Therapy End Date

Eli Lilly and Company - Global Patient Safety **Case Number:**

Concomitant Substances (include prescription, OTC, and herbal)	
☐ Current Alcohol	☐ Past Alcohol
What was the amount of Beer consumed? ounces/ ml (Please check the box next to the correct frequency)	☐ Daily ☐ Weekly ☐ Monthly ☐ Yearly
What was the amount of Wine consumed? ounces/ ml (Please check the box next to the correct frequency)	☐ Daily ☐ Weekly ☐ Monthly ☐ Yearly
What was the amount of Spirits consumed? ounces/ ml (Please check the box next to the correct frequency)	☐ Daily ☐ Weekly ☐ Monthly ☐ Yearly
☐ Current Tobacco	☐ Past Tobacco
☐ Current Cocaine/Methamphetamine	☐ Past Cocaine/Methamphetamine
☐ Others:	

Relevant Laboratory Tests	**Normal Range for Your Institution**	**Baseline Value for Patient**	**Abnormal Value**	**Improvement Value**
		Date:	**Date:**	**Date:**
AST (SGOT)				
ALT (SGPT)				
Total Bilirubin				
Direct Bilirubin				
Alk. Phos.				
GGT				
LDH				
PT-INR				
PT				
Ammonia				
Albumin				
CPK				
Creatinine				
WBC				
Hemoglobin				
Platelet Count				
Blood Alcohol Level				
Urine Toxicology Screen				
Acetaminophen Level				

Eli Lilly and Company - Global Patient Safety **Case Number:**

Serologic Studies (check positive) (Please include values if applicable)	
☐ Anti-mitochondrial Antibody (AMA)	☐ Hepatitis A Virus Antibody IgM (anti-HAV IgM)
☐ Anti-nuclear Antibody (ANA)	☐ Hepatitis A Virus Antibody IgG (anti-HAV IgG)
☐ Anti-liver Kidney Microsomal (antiLKM)	☐ Hepatitis B Virus Core Antibody IgM (anti-HBc IgM)
☐ Anti-actin	☐ Hepatitis B Virus Surface Antibody (anti-HBs)
☐ Anti-smooth Muscle Antibody (ASMA)	☐ Hepatitis B Virus Surface Antigen (HBs Ag)
☐ Cytomegalovirus (CMV) Antibody IgM	☐ Hepatitis B Virus DNA (HBV DNA)
☐ Ebstein Barr (EBV) Serology IgM	☐ Hepatitis C Virus Antibody (anti-HCV)
☐ Ebstein Barr (EBV) Serology IgG	☐ Hepatitis C Virus RNA (HCV RNA)
☐ Other:	☐ Hepatitis E Virus Antibody IgM (anti-HEV IgM)
☐ Other:	☐ Hepatitis E Virus Antibody IgG (anti-HEV IgG)
Please list studies that were completed and were negative:	

Other Study	**Results**
Liver Biopsy	
Hepatic Ultrasound	
MRI	
Magnetic Resonance Cholangiopancreatography (MRCP)	
Magnetic Resonance Cholangiography (MRC)	
CT Scan	
Other:	

Treatment provided (please describe)

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender: ☐ M ☐ F ☐ Unknown	Race: ☐ Caucasian ☐ Asian ☐ Black ☐ Other	Weight: ☐ lb ☐ kg	Height: ☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

⊞

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Please provide brief explanation:

Cancer/Neoplasm

Primary Diagnosis for the reported event(s):	
Hospitalization for this event? ☐ No ☐ Yes	
☐ Please specify primary site:	
☐ Neoplasm (benign mass/lesions)	☐ Possible malignant tumor – not yet confirmed
☐ Malignant tumor (please attach copy of pathology report or provide the information of Stage/Grade, Staging classification and tissue source):	
Concomitant Medications/Substances (please include prescription, OTC, and herbal)	
Relevant Tests/Studies (please attach copy of pathology report, if available)	
Study	**Result**
Histopathology (please indicate stage/grade, staging classification and tissue source)	
Ultrasound	
CAT Scan	
MRI	
Other:	
Medical History/Risk Factors	
☐ Cancer:	☐ Family history of cancer:
☐ Chemotherapy:	☐ Radiation therapy
☐ Estrogen use: years	☐ Tobacco use
☐ Diabetes mellitus	☐ Obesity
☐ Alcohol	☐ No known predisposing factors
☐ Immunosuppression:	☐ Environmental risk:
☐ Other (please describe):	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Treatment provided (please describe):

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender: ☐ M ☐ F ☐ Unknown	Race: ☐ Caucasian ☐ Asian ☐ Black ☐ Other	Weight: ☐ lb ☐ kg	Height: ☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

⊞

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Cardiac Disorders			
Primary Diagnosis for the reported event(s):			
☐ Chest Pain/Angina	☐ Myocardial Infarction	☐ Arrhythmia	☐ Other – please describe:
Hospitalization for this event? ☐ No ☐ Yes			
Presenting Signs/Symptoms			
☐ Heart Rate:		☐ Blood Pressure:	
☐ Palpitations		☐ Shortness of Breath	
☐ Syncope		☐ Chest Pain (please specify):	
☐ Cardiac Exam:			
☐ Pulmonary Exam:			
☐ Other (please specify):			
Relevant Medical History (please specify if needed)			
☐ Atrial Arrhythmia		☐ Ventricular Arrhythmia	
☐ Conduction Disorders		☐ Congenital Heart Abnormalities	
☐ Cardiovascular Disease		☐ Hypertension	
☐ Cardiovascular Infection		☐ Cardiac Surgeries	
☐ Pulmonary Disease		☐ Pulmonary Embolism	
☐ Metabolic Disorders		☐ Psychiatric/Emotional Disorders	
☐ Pericarditis		☐ Syncope	
☐ Poor compliance with BP/Cardiac Meds		☐ Dizziness	
☐ Family History of cardiac disease, congenital QT prolongation, premature cardiac death		☐ Substance Abuse	
☐ Other (please specify):			
Historic Drugs (please specify)			
☐ Antiarrhythmics:		☐ Antihypertensives:	
☐ Psychiatric Medications:		☐ Antibiotics:	
☐ Others:			
Concomitant Meds (include prescription, substance, OTC, and herbal)			
☐ Nitrates/Nitrites		☐ Alpha Blocker	
☐ ED Medication (please specify):		☐ Others:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Relevant Laboratory Tests	Normal Range for Your Institution	Baseline Value for Patient	Abnormal Value	Improvement Value
		Date:	Date:	Date:
Cardiac Enzyme (please specify):				
Serum Potassium				
Serum Calcium				
pO2				
O2 Saturation				

Other Diagnostic Tests	Results		
EKG (Q Waves)/EKG (QTC Interval)			
Myocardial Scan			
Echocardiogram (ECHO)			
Coronary Angiography			
Exercise Stress Test			
QT Interval (milliseconds)			
QTc (Corrected Value)			
How was QT Interval measured?	☐ Machine	☐ Manually	☐ Other
QT Correction Formula	☐ Bazett	☐ Fridericia	☐ Other
Other:			

Treatment	
☐ Cardioversion/Defibrillation	☐ Treatment not required
☐ Medication (please specify):	☐ Ablation
☐ Other (please specify):	

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender:	Race:	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Cerebrovascular Accident
Primary Diagnosis for the reported event(s):

Eli Lilly and Company - Global Patient Safety **Case Number:**

Hospitalization for this event? ☐ No ☐ Yes		
Concomitant Medications/Substances (please include prescription, OTC and herbal)		
Presenting Signs/Symptoms		
Onset Date:	End Date:	
Impairments:		
☐ Paralysis (specify):	☐ Dysarthria	☐ Impaired consciousness
☐ Weakness (specify):	☐ Visual field defect	☐ Seizure
☐ Dysphagia	☐ Aphasia	☐ Other findings:
Severity		
☐ No/Mild	☐ Moderate	☐ Severe
Relevant Medical History		
☐ Diabetes	☐ Artrial fibrillation	☐ Head trauma
☐ Smoking	☐ Hypertension	☐ Prior stroke
☐ Myocardial infarction	☐ Hyperlipidemia	☐ Other (please specify):

Relevant Laboratory Tests	Normal range for your institution	Baseline value for patient	Abnormal value	Improvement value
		Date:	Date:	Date:
Hemoglobin				
WBC				
Platelet Count				
Glucose				
INR				
aPTT				
Thrombin Time				
Fibrinogen				
Other:				

Other Tests	Results
CT	
MRI	
Angiography	
EEG	
Other:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Treatment		
☐ Support and organization	☐ Thrombolytic agent	☐ Ablation
☐ Antiplatelet agent	☐ Anticoagulant	Other:

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Not applicable.