EU Risk Management Plan (Version 0.4)

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: 0.4

Data lock point for this RMP: 06 December 2021

Date of final sign off: See Cover Page

Rationale for submitting an updated RMP: In response to the CHMP request dated 23 March 2023, an update to Table Part V.1 is provided along with additional information in SVII.3 to match revisions in the SmPC. Any company confidential information and privacy data have been eliminated.

Summary of significant changes in this RMP:

- Details in SVII.3 related to evaluation for TB infection and monitoring of patients during and after treatment is provided to match requested revisions in the SmPC.
- At the request of CHMP, an update to Table Part V.1 is provided to match the revisions in the SmPC.

Other RMP versions under evaluation

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- Submitted on: Not applicable
- Procedure number: Not applicable

Details of the currently approved RMP

- Version number: Not applicable
- Approved with procedure: Not applicable
- Date of approval (opinion date): Not applicable

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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<td>Term</td>
<td>Definition</td>
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</tr>
<tr>
<td>AE</td>
<td>adverse event</td>
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<tr>
<td>ADR</td>
<td>adverse drug reaction</td>
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<tr>
<td>AIH</td>
<td>autoimmune hepatitis</td>
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<tr>
<td>ALP</td>
<td>alkaline phosphatase</td>
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<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
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<tr>
<td>ASA</td>
<td>amino salicylic acid</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>CCV</td>
<td>cerebrocardiovascular</td>
</tr>
<tr>
<td>CD</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>CHD</td>
<td>coronary heart disease</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>COVID-19</td>
<td>coronavirus disease 2019</td>
</tr>
<tr>
<td>CRC</td>
<td>colorectal cancer</td>
</tr>
<tr>
<td>DILI</td>
<td>drug-induced liver injury</td>
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<tr>
<td>DVT</td>
<td>deep venous thrombosis</td>
</tr>
<tr>
<td>EAIR</td>
<td>exposure-adjusted incidence rate</td>
</tr>
<tr>
<td>EIMs</td>
<td>extraintestinal manifestations</td>
</tr>
<tr>
<td>ePPND</td>
<td>enhanced pre- and post-natal development</td>
</tr>
<tr>
<td>GGT</td>
<td>gamma-glutamyl transpeptidase</td>
</tr>
<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
</tr>
<tr>
<td>HCV</td>
<td>hepatitis C virus</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>ICH</td>
<td>International Council for Harmonisation</td>
</tr>
<tr>
<td>IBD</td>
<td>inflammatory bowel disease</td>
</tr>
<tr>
<td>IgG</td>
<td>immunoglobulin</td>
</tr>
<tr>
<td>IL</td>
<td>interleukin</td>
</tr>
<tr>
<td>IR</td>
<td>incidence rate</td>
</tr>
<tr>
<td>IRR</td>
<td>incidence rate ratio</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>MACE</td>
<td>major adverse cardiac event</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>Miri</td>
<td>mirikizumab</td>
</tr>
<tr>
<td>NAFLD</td>
<td>non-alcoholic fatty liver disease</td>
</tr>
<tr>
<td>NMSC</td>
<td>non-melanoma skin cancer</td>
</tr>
<tr>
<td>NOAEL</td>
<td>no-observed-adverse-effect level</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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<td>------</td>
<td>------------</td>
</tr>
<tr>
<td>PE</td>
<td>pulmonary embolism</td>
</tr>
<tr>
<td>Ps</td>
<td>psoriasis</td>
</tr>
<tr>
<td>PSC</td>
<td>primary sclerosing cholangitis</td>
</tr>
<tr>
<td>PY</td>
<td>person years</td>
</tr>
<tr>
<td>PYE</td>
<td>patient years of exposure</td>
</tr>
<tr>
<td>Q8W</td>
<td>every 8 weeks</td>
</tr>
<tr>
<td>RMP</td>
<td>risk management plan</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SC</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>SmPC</td>
<td>summary of product characteristics</td>
</tr>
<tr>
<td>SIR</td>
<td>standardized incidence ratio</td>
</tr>
<tr>
<td>SMR</td>
<td>standardized mortality ratio</td>
</tr>
<tr>
<td>TEAE</td>
<td>treatment-emergent adverse event</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TNF</td>
<td>tumour necrosis factor</td>
</tr>
<tr>
<td>UC</td>
<td>ulcerative colitis</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
<tr>
<td>VTE</td>
<td>venous thromboembolism</td>
</tr>
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</table>
## Part I: Product(s) Overview

### Table Part I.1. Product Overview

<table>
<thead>
<tr>
<th>Active substance(s) (INN or common name)</th>
<th>Mirikizumab (LY3074828)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacotherapeutic group(s) (ATC Code)</td>
<td>Not available</td>
</tr>
<tr>
<td>Marketing authorisation holder</td>
<td>Eli Lilly and Company</td>
</tr>
<tr>
<td>Medicinal products to which this RMP refers</td>
<td>1</td>
</tr>
<tr>
<td>Invented name(s) in the EEA</td>
<td>Omvoh</td>
</tr>
<tr>
<td>Marketing authorisation procedure</td>
<td>Centralised</td>
</tr>
</tbody>
</table>

**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. The IV infusion and the SC injection are composed of mirikizumab and the inactive ingredients sodium citrate dihydrate, citric acid anhydrous, sodium chloride, polysorbate 80, and water for injection.

**Hyperlink to the Product Information**

The current PI is included in eCTD sequence 1.3.1

**Indication(s) in the EEA**

**Current:** Not applicable

**Proposed:** UC

**Dosage in the EEA**

**Current:** Not applicable

**Proposed:**

The recommended mirikizumab dose regimen has 2 parts:
- Induction dosing of 300 mg mirikizumab infused intravenously for at least 30 minutes at Weeks 0, 4, and 8.
- Maintenance dosing of 200 mg mirikizumab injected subcutaneously every 4 weeks, starting at Week 12. A full maintenance dose is two 100 mg pre-filled syringes or two 100 mg pre-filled pens.

**Pharmaceutical form(s) and strengths**

**Current:** Not applicable

**Proposed:** The medicinal drug product mirikizumab for IV infusion is supplied as a concentrate for 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).
| Is/will the product be subject to additional monitoring in the EU? | Yes |

The medicinal drug product mirikizumab for SC injection is supplied as a 100 mg/mL solution in a 1-mL pre-filled syringe and a 1 mL 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.

Abbreviations: ATC = anatomical therapeutic chemical; CHO = Chinese hamster ovary; 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).

Incidence rates 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] [proposed] 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-institutionalized 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/ethnicity**

In terms of race, in a nationally representative annual survey of the non-institutionalized 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 (OR = 0.45; 95% CI = 0.44-0.46) patients 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, and small molecule Janus kinase inhibitors including tofacitinib. 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, mucus discharge, 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

Psychiatric disorders

Ulcerative colitis has been associated with various psychiatric disorders including depression, anxiety, and suicidality or suicidal ideation.

Depression

The prevalence of depression among patients with UC ranges from 11.7% (Ramos-Rodriguez et al. 2018) to 32% of patients (Kochar et al. 2018) with an estimated pooled prevalence of 24.0%; however, there was significant heterogeneity among the studies (I² = 97.0%) (Barberio et al. 2021). Studies also show a bidirectional association between UC and depression. Depression has been found to be associated with a significantly increased risk of developing UC after controlling for demographic and clinical covariates (adjusted HR = 2.23, 95% CI = 1.92-2.60) (Frolkis et al. 2019). Conversely, several studies have found UC to be associated with a significantly increased risk for depression (Bernstein et al. 2019; Choi et al. 2019a; Irving et al. 2021; Tarar et al. 2022). One study (Bernstein et al. 2019) found that patients with UC had a significantly higher incidence of depression (IRR = 1.43; 95% CI = 1.24-1.64).
Anxiety

In a meta-analysis involving 22 studies, the pooled prevalence of anxiety symptoms among patients with UC was 34.2% but with significant heterogeneity among the studies ($I^2 = 95.6\%$) (Barberio et al. 2021). UC has also been found to be associated with a significantly increased risk for anxiety disorder ($IRR = 1.27$, 95% CI 1.11-1.44) (Bernstein et al. 2019). Similarly, another study (Choi et al. 2019a) found patients with UC had a significantly increased risk for anxiety ($HR = 2.06$, 95%CI 1.74-2.44).

Bipolar disorder

Ulcerative colitis has been associated with an increased risk for bipolar disorder. In population-based studies using administrative health data in Canada and Sweden, patients with UC had an increased risk for bipolar disorder ($IRR = 1.82$, 95% CI 1.33-2.50 and $HR = 1.2$, 95% CI 1.1-1.4, respectively) (Bernstein et al. 2019; Ludvigsson et al. 2021).

Suicidality

Results from 2 large population-based studies (Gradus et al. 2010) and (Jess et al. 2013) from Denmark found patients with UC to have a significantly increased risk of completed suicide compared to a general population (OR = 1.9, 95% CI = 1.4-2.4, and $HR = 1.26$, 95% CI = 1.08-1.49, respectively). However, a large cohort study in Canada did not report an increased risk of completed suicide for patients with UC compared to a general population ($HR = 0.94$, 95% CI 0.42-2.12) (Bernstein et al. 2015).

Cardiovascular disorders

Cerebrocardiovascular events

The IRs for various cerebrovascular events among patients with UC range from 1.98 to 4.56 per 1000 PY (Huang et al. 2014; Kristensen et al. 2014; Choi et al. 2019b). Specifically, the IRs for stroke among UC patients range from 2.23 to 4.45 per 1000 PY (Huang et al. 2014; Kristensen et al. 2014; Choi et al. 2019b). Several studies have found UC to be associated with an increased risk of stroke (Keller et al. 2014; Xiao et al. 2015; Yuan et al. 2016; Chen et al. 2021). One study using health insurance data from Taiwan found UC to be associated with a significantly increased risk for stroke ($HR = 2.045$, 95% CI = 1.374-3.043) compared to control subjects (Keller et al. 2014). Similarly, in a nationwide Swedish register-based study, UC was found to be associated with a significantly increased risk for both haemorrhagic and ischaemic stroke ($SIR = 1.37$, 95% CI = 1.13-1.66 and $SIR = 1.21$, 95% CI = 1.21-1.31, respectively) (Zöller et al. 2012). However, other studies found no significant association between UC and the risk for stroke (Dregan et al. 2014; Kristensen et al. 2014; Choi et al. 2019b). For example, there was no statistically significant association between UC and the risk for stroke among patients in Korea ($HR = 1.05$; 95% CI 0.95-1.16) (Choi et al. 2019b) as well as in Denmark ($IRR = 1.10$, 95% CI = 0.99-1.22) (Kristensen et al. 2014).
Coronary heart disease

The incidence of CHD was found to be higher among patients with UC (25.3/10 000 PY) compared to matched general population controls (17.8/10 000 PY) and patients with UC were found to have a significantly increased risk for CHD when compared to the general population (IRR = 1.26, 95%CI = 1.05-1.51) (Bernstein et al. 2008). Similarly, another study found patients with UC to have a higher risk for CHD compared to individuals without IBD (IRR = 1.22, 95% CI = 1.13-1.32) (Rungoe et al. 2013). However, one study found no significant association between UC and the risk for CHD (HR = 1.13, 95%CI = 0.95-1.35) (Dregan et al. 2014).

The IR for MI was found to be higher among patients with UC (3.42/1000 PY) compared to matched general population controls in Denmark (1.95/1000 PY) and patients with UC were found to have a significantly higher risk for MI compared to the general population (RR = 1.17, 95% CI = 1.03-1.33) (Kristensen et al. 2013). However, no significant association between UC and the risk for MI among patients in Korea (HR = 1.11, 95%CI = 0.99-1.24) (Choi et al. 2019).

Venous thromboembolism

The incidence of VTE, which includes DVT and PE, among patients with UC ranges from 11/10 000 PY to 24/10 000 PY (Kappelman et al. 2011; Isene et al. 2014; Vegh et al. 2015) and the incidence of VTE among patients with UC (24/10 000 PY) was found to be higher than the rate in controls without UC (13/10 000 PY) (Kappelman et al. 2011). In addition, several studies have found UC to be associated with a significantly higher risk for VTE after adjustment for potential confounders. In one study, UC was found to be associated with a significantly higher risk of any VTE (HR = 1.9; 95%CI = 1.8-2.0) as well as unprovoked VTE or VTE occurring in the absence of malignancy or recent surgery, fracture or pregnancy (HR = 1.5; 95%CI = 1.4-1.7) when compared to controls (Kappelman et al. 2011). Similarly, one study found UC to be associated with a significantly higher risk for VTE when compared to controls without UC or CD (RR = 1.64, 95%CI = 1.62-1.66) (Saleh et al. 2011) while another found an HR of 1.27 (95%CI = 1.10-1.45) (Galloway et al. 2020). A metanalysis of these studies indicated a significant pooled association between UC and risk for VTE (RR = 2.57; 95%CI = 2.02-3.28). However, there was significant heterogeneity between the studies ($I^2 = 94.6\%$) (Yuhara et al. 2013).

Deep venous thrombosis

Reported IRs of DVT among patients with UC range from 14/10 000 PY to 30/10 000 PY (Bernstein et al. 2001a; Kappelman et al. 2011; Liu et al. 2021) and the incidence of DVT was found to be higher among UC patients (14.3/10 000 PY) when compared to controls without UC (8.2/10 000 PY) (Kappelman et al. 2011). Several studies have also reported a significant association between UC and the risk for any DVT (HR = 1.8; 95% CI = 1.6-2.0 [Kappelman et al. 2011], IRR = 2.77; 95% CI = 2.07-3.69 [Bernstein et al. 2001a], and RR = 1.77; 95% CI = 1.74-1.80 [Saleh et al. 2011]). In addition, UC has also been associated with an increased risk for unprovoked DVT or DVT occurring in the absence of malignancy or recent surgery, fracture or pregnancy, HR = 1.5 (95% CI = 1.3-1.7) (Kappelman et al. 2011).
Pulmonary embolism

The incidence of PE among patients with UC has been estimated at 5 to 10/10 000 PY (Kappelman et al. 2011; Liu et al. 2021) and it was found to be higher among patients with UC (10/10 000 PY) compared to non-IBD controls (5/10 000 PY) (Kappelman et al. 2011). Ulcerative colitis has also been associated with a significantly higher risk for PE. One study in Danish children and adults (Kappelman et al. 2011) found UC to be associated with a significantly higher risk for both any PE (HR = 2.0, 95% CI = 1.8-2.2) and unprovoked PE or PE occurring in the absence of malignancy or recent surgery, fracture, or pregnancy (HR = 1.6, 95% CI = 1.4-1.9). Another study (Saleh et al. 2011) also reported a significantly higher risk of PE among UC patients (RR = 1.40, 95% CI = 1.37-1.44).

Malignancy

Studies examining the association between UC and the overall risk of malignancies have produced mixed results. Although some studies have found UC to be associated with a significantly increased risk of malignancies overall (Jussila et al. 2013; Burisch et al. 2022), other studies found no significant increase (Van den Heuvel et al. 2016; Taborelli et al. 2020).

Reported IRs of CRC among patients with UC range from 66.4 per 100 000 PY in a population-based prospective cohort from North Jutland County, Denmark (Jess et al. 2013) to 250 per 100 000 PY in a prospective French Population-based registry study of patients above 60 years of age (Cheddani et al. 2016). Studies examining the association between UC and the risk for CRC based on estimates of the SIR have produced mixed results with some reporting an increased SIR for CRC (Jussila et al. 2013; Manninen et al. 2013; Hovde et al. 2017) while others found no significantly increased SIR (Jess et al 2013; So et al. 2017; Taborelli et al. 2020). However, the incidence of CRC was found to be consistently significantly higher among UC patients when compared to non-IBD controls (Herrinton et al. 2012; King et al. 2020; Olén et al. 2020). The incidence of CRC among UC patients (135.3/100 000 PY) in the UK was found to be significantly higher compared to the rate (94.9/100 000 PY) in non-IBD controls (HR = 1.40, 95% CI = 1.23-1.59). Similar findings were reported in the US (IRR = 1.6, 95% CI = 1.3-2.0) (Herrinton et al. 2012), Denmark (HR = 1.30, 95% CI = 1.17-1.45) (Olén et al. 2020), Sweden (HR = 1.87, 95% CI = 1.75-2.00), and both Sweden and Denmark combined (HR = 1.66, 95% CI = 1.57-1.76). A meta-analysis of 116 studies estimated the overall prevalence of CRC in any patient with UC was 3.7% (95% CI = 3.2-4.2%) (Eaden et al. 2001). Risk factors for CRC among patients with UC include younger age of UC onset, increasing age, disease severity and duration, pan sclerosing cholangitis and genetics or family history of CRC (Lakatos et al. 2006; Olén et al. 2020).

Patients with UC have also been found to have increased risk for various extra intestinal malignancies including non-melanoma skin cancer (Burisch et al. 2022), melanoma (Hovde et al. 2017; Burisch et al. 2022), pancreatic cancer (Burisch et al. 2022), thyroid cancer (Hovde et al. 2017; Burisch et al. 2022), and lymphoma. The risk of lymphoma among UC patients has been found to be particularly higher during thiopurine therapy (Long et al. 2012; Khan et al. 2013; Singh et al. 2014b; Hagen et al. 2018). A 4-fold increased risk of lymphoma was found among...
UC patients during treatment with thiopurines when compared to patients not treated with thiopurines (HR = 4.2, 95% CI = 2.5-6.8) but the risk was no longer increased after patients discontinued thiopurine therapy (HR = 0.5, 95% CI = 0.2-1.3) (Khan et al. 2013).

Hepatobiliary disorders

Ulcerative colitis has been associated with various hepatobiliary disorders including transient elevations of liver enzymes with no known cause and persistent elevations most commonly due to PSC, AIH, cholelithiasis, and NAFLD (Gizard et al. 2014).

Elevated liver enzymes

In a retrospective case series analysis of 141 patients with UC, an increase in serum aminotransferases (ALT, AST, ALP, GGT, or total bilirubin) was detected in 19.9% of the patients with UC (Cappello et al. 2014). In a case control study that included 317 patients with UC, the estimated prevalence of elevated ALT, GGT, and ALP ≥2xULN were 5.7%, 5.7%, and 3.8%, respectively (Riegler et al. 1998), whereas in a case series study of 534 patients with UC, the prevalence rates of elevated ALP and ALT levels >2xULN based on the highest recorded value during follow-up were 6% and 10%, respectively (Aitola et al. 1994). In a population-based cohort study that used UK biobank data, patients with UC were found to have a significantly higher risk for elevated ALT ≥2xULN (OR = 1.86, 95% CI = 1.21-2.87), GGT ≥2xULN (OR = 1.47, 95% CI = 1.30-1.66), GGT ≥5xULN (OR = 1.89, 95% CI = 1.21-2.94), and ALP ≥2xULN (OR = 4.22, 95% CI = 2.81-6.36) compared to controls (Voss et al. 2021).

Primary sclerosing cholangitis

The incidence of PSC among patients with UC was estimated at 8.4 per 10 000 PY and it was found to be higher than the rate (1.2 per 10 000 PY) in controls (Burisch et al. 2019). The estimated prevalence of PSC among patients with UC ranges from 0.76% to 5.4% (Gizard et al. 2014) and approximately 70% of patients with PSC have associated IBD, predominantly (>75%) UC (De Vries et al. 2015). In addition, UC has been associated with a significantly increased risk for PSC overall (IRR = 6.85, 95% CI = 4.27-10.97) (Burisch et al 2019) and in both men (OR = 30.3, 95% CI = 11.0-83.0) and women (OR = 9.5, 95% CI = 2.7-32) separately, when compared to the general population (Bernstein et al. 2001b).

Autoimmune hepatitis

In a cross-sectional study of 31 066 patients with UC matched to 60 951 controls in the Danish National Patient Registries, the prevalence of AIH was higher among patients with UC (0.31%) compared to the controls (0.04%) and UC was found to be associated with a significantly increased risk for AIH (OR = 8.6, 95% CI = 5.4-13.6) (Halling et al. 2017). Similarly, in a retrospective analysis of a large population-based, commercial electronic health record database in the US, the risk for AIH was found to be significantly higher among patients with UC compared to controls (OR = 10.50, 95% CI = 9.55-11.55) (Tunio et al. 2021).
Cholelithiasis

The incidence of cholelithiasis has been found to be higher among patients with UC (0.75/100 PY) compared to matched controls (0.61/100 PY) (Parente et al. 2007). Estimates of the prevalence of cholelithiasis among patients with UC range from 4.6% to 36.4% (Gizard et al. 2014) and in a population-based cohort study that used the UK biobank data, the prevalence of cholelithiasis among patients with UC (5.9%) was significantly higher than the prevalence in the controls (3.9%) (p<.001). Ulcerative colitis has also been associated with a significantly increased risk for cholelithiasis after adjustment for potential confounders (OR = 1.57, 95% CI = 1.37-1.81) (Voss et al. 2021).

Non-alcoholic fatty liver disease

The prevalence of NAFLD among patients with UC ranges from 1.5% to 55% with an estimated mean prevalence of 23% (Gizard et al. 2014). In addition, UC was found to be associated with more than a 4-fold increased risk for mild steatosis (OR = 4.80, 95% CI = 1.64-14.04) and 7-fold increased risk for moderate to severe steatosis (OR = 7.49, 95% CI = 2.36-23.76), and this association was independent from other risk factors such as glucose and body mass index (Mancina et al. 2020).

Other autoimmune diseases

In addition to PSC and AIH, there is a recognized increased incidence of other autoimmune conditions in patients with UC. In particular, patients with UC had approximately a 2- to 2.5-fold increased risk of systemic rheumatoid connective tissue disorders such as rheumatoid arthritis, fibromyalgia, ankylosing spondylitis, systemic lupus erythematosus; endocrine disorders such as diabetes type I, Addison disease, Graves’ disease, Hashimoto thyroiditis, and other digestive conditions including celiac disease and pernicious anaemia compared to controls (Wilson et al. 2016). Women are particularly at increased risk of developing additional autoimmune diseases.

The prevalence of comorbid autoimmune conditions among UC patients varies across studies. A review of IBD patients from a clinic in Switzerland identified the prevalence of following various autoimmune conditions among UC patients: arthritis (21%), ankylosing spondylitis (2%), pyoderma gangrenosum (2%), erythema nodosum (3%), and Ps (1%) (Vavricka et al. 2011). Another study of IBD patients in Greece identified the prevalence of following various autoimmune conditions among patients with UC: arthritis (14.7%), ankylosing spondylitis (0.6%), erythema nodosum (2.8%), pyoderma gangrenosum (0.9%), and Ps (2.1%) (Karmiris et al. 2016).
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 post-natal 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 neutralization 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 post-natal 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 up to 30-fold based on the induction dose of 300 mg IV and up to 100-fold at the maintenance dose of 200 mg SC for the UC indication.
Module SIII - Clinical Trial Exposure

Table SIII.1. Duration of Exposure

In this RMP, the safety of mirikizumab is evaluated in 2 integrated datasets:

- All Mirikizumab Exposures Integrated Analysis Set, comprised of all clinical trial data in patients with UC, CD, and Ps 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.

<table>
<thead>
<tr>
<th>Duration of exposure</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Mirikizumab Exposures Integrated Analysis Set</td>
<td></td>
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<tr>
<td>&gt;0 week to &lt; 4 weeks</td>
<td>35</td>
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<tr>
<td>≥4 weeks to &lt;8 weeks</td>
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<td>≥16 weeks to &lt;24 weeks</td>
<td>111</td>
</tr>
<tr>
<td>≥24 weeks to &lt;32 weeks</td>
<td>233</td>
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<tr>
<td>≥32 weeks to &lt;52 weeks</td>
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<tr>
<td>≥52 weeks to &lt;104 weeks</td>
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<td><strong>Total patient year</strong></td>
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</table>

<table>
<thead>
<tr>
<th>Duration of exposure</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
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<td>UC Mirikizumab Exposures Integrated Analysis Set</td>
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</tr>
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<td>&gt;0 week to &lt; 4 weeks</td>
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</tr>
<tr>
<td>≥4 weeks to &lt;8 weeks</td>
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<td>≥8 weeks to &lt;12 weeks</td>
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<td><strong>Total patient year for UC</strong></td>
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Abbreviations: miri = mirikizumab; UC = ulcerative colitis.
Source: /lillyce/prd/ly3074828/regulatory/subm_uc/output/shared/tfl/t_ex_expo_amiri_allm.rtf
Table SIII.2. Age Group and Gender

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<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Adults (&lt;65 years)</td>
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<td>1199</td>
</tr>
<tr>
<td>Elderly people</td>
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<td>117</td>
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<tr>
<td>65-74 years</td>
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</tr>
<tr>
<td>75-84 years</td>
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<table>
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Abbreviations: miri = mirikizumab; UC = ulcerative colitis.

Source: /lillyce/prd/ly3074828/regulatory/subm_uc/output/shared/tfl/ad_t_ex_expo_byagesex_amiri_allm.rtf
### Table SIII.3. Dose

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<td>30 miri PRN SC</td>
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<tr>
<td>30 miri Q8W SC</td>
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<tr>
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<td>100 miri PRN SC</td>
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<td>100 miri Q8W SC</td>
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<tr>
<td>200 miri Q12W SC</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1442</strong></td>
<td><strong>2250.9</strong></td>
</tr>
</tbody>
</table>

Abbreviations: IV = intravenous; miri = mirikizumab; PRN = as needed; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous; UC = ulcerative colitis.

Source: /lillyce/prd/ly3074828/regulatory/subm_uc/output/shared/tfl/ad_t_ex_expo_bytrtdos_amiri_allm.rtf.
### Table SIII.4. Ethnic Origin

<table>
<thead>
<tr>
<th>Ethnic origin</th>
<th>Patients</th>
<th>Patient year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Mirikizumab Exposures Integrated Analysis Set</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>78</td>
<td>171.6</td>
</tr>
<tr>
<td>Asian</td>
<td>757</td>
<td>1471.1</td>
</tr>
<tr>
<td>Black or African American</td>
<td>69</td>
<td>155.5</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>5</td>
<td>9.3</td>
</tr>
<tr>
<td>White</td>
<td>2868</td>
<td>5965.0</td>
</tr>
<tr>
<td>Multiple</td>
<td>10</td>
<td>19.6</td>
</tr>
<tr>
<td>Missing</td>
<td>11</td>
<td>9.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3798</strong></td>
<td><strong>7801.3</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnic origin</th>
<th>Patients</th>
<th>Patient year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UC Mirikizumab Exposures Integrated Analysis Set</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>11</td>
<td>10.1</td>
</tr>
<tr>
<td>Asian</td>
<td>304</td>
<td>418.0</td>
</tr>
<tr>
<td>Black or African American</td>
<td>19</td>
<td>36.4</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>White</td>
<td>1094</td>
<td>1773.8</td>
</tr>
<tr>
<td>Multiple</td>
<td>3</td>
<td>2.1</td>
</tr>
<tr>
<td>Missing</td>
<td>10</td>
<td>8.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1442</strong></td>
<td><strong>2250.9</strong></td>
</tr>
</tbody>
</table>

Abbreviations: miri = Mirikizumab; UC = ulcerative colitis.

Source: /lillyce/prd/ly3074828/regulatory/subm_uc/output/shared/tfl/ad_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. Phase 2 trials in patients 2 to below 18 years of age are currently ongoing and Phase 3 studies in this paediatric age group are planned.

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

**Rationale:** Section 8.4 of the prescribing information will clearly state that the safety and efficacy of mirikizumab in children and adolescents of 2 to below 18 years of age have not yet been established. Additionally, approved, alternative therapeutic options are available for the treatment of UC in paediatric patients. It was agreed with Regulatory Agencies (US and EU) to start paediatric development once a positive risk-benefit in adults has been established. Phase 2 trials in this population are currently ongoing.

**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 population. There were 28 pregnancies from maternal exposure and 41 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 and local labels.

**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, those patients should not initiate treatment 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.

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, local labelling will advise 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

<table>
<thead>
<tr>
<th>Type of special population</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women</td>
<td>Pregnancy was an exclusion criterion in the clinical development programme</td>
</tr>
<tr>
<td>Breastfeeding women</td>
<td>Not included in the clinical development programme</td>
</tr>
<tr>
<td>Patients with relevant comorbidities:</td>
<td>Mirikizumab has not been specifically studied in patients with renal, hepatic or cardiovascular impairment.</td>
</tr>
<tr>
<td>Patients with hepatic impairment</td>
<td></td>
</tr>
<tr>
<td>Patients with renal impairment</td>
<td></td>
</tr>
<tr>
<td>Patients with cardiovascular impairment</td>
<td></td>
</tr>
<tr>
<td>Immunocompromised patients</td>
<td>Immunocompromised patients were excluded from mirikizumab clinical trials</td>
</tr>
<tr>
<td>Patients with a disease severity different from inclusion criteria in clinical trials</td>
<td>The clinical development programme included patients with moderately to severely active UC. Patients with mild disease were not specifically studied.</td>
</tr>
<tr>
<td>Population with relevant different ethnic and racial origin</td>
<td>Mirikizumab Phase 3 clinical trials enrolled patients globally. Patients of non-White origin were included in the clinical trials.</td>
</tr>
<tr>
<td></td>
<td>Of the treated population, 18.4% were Hispanic or Latino, 80.9% were non-Hispanic/non-Latino, and ethnicity data were missing for 0.7%; 75.5% were white or Caucasian, 19.9% were Asian, 2.1% 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 0.3%. 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.</td>
</tr>
<tr>
<td>Subpopulations carrying relevant genetic polymorphisms</td>
<td>Not applicable. Patient-level genetic polymorphisms were not specifically studied in the clinical development programme.</td>
</tr>
<tr>
<td>Type of special population</td>
<td>Exposure</td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Elderly</td>
<td>Mirikizumab clinical trials enrolled patients 85 years and younger in age, including 7.6% were 65 to 74 years, and 1.0% were 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.</td>
</tr>
<tr>
<td>Other</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
Module SV - Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

Mirikizumab has not yet obtained marketing authorisation. Therefore, no post-authorisation exposure data are available yet.

SV.1.1 Method Used to Calculate Exposure
Not applicable.

SV.1.2 Exposure
Not applicable.
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 Ps, 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 Ps) 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 ≥3xULN and maximum total bilirubin ≥2xULN 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 Ps, 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 ≥5xULN treated with mirikizumab compared to placebo (0.8% and 0%, respectively, in Study AMBG) and AST ≥5xULN 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 unknow 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 Ps 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 Ps. 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:

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

Abbreviation: n = number of participants within each specific category

a One case of elective abortion was reported in a healthy volunteer from Study AMBD.
b One case of pregnancy with an unknown outcome was reported in a healthy volunteer from Study AMBW.

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 an immunomodulatory drug and, as such, may increase the risk of developing an infection or exacerbate an existing infection.

Evidence source(s) and strength of evidence:

In patients with UC across the Phase 2 and Phase 3 studies, serious infections (n = 33, 2.3%) were reported commonly during treatment with mirikizumab. When including time off mirikizumab and the post-treatment follow-up period, serious infections (n = 39, 2.7%) were also reported commonly. Although the majority of patients recovered, serious infections due to coronavirus or COVID-19 infections resulted in the deaths of 3 patients with UC, 1 while receiving mirikizumab and 2 while off mirikizumab.

Across all mirikizumab exposures in Phase 2 and Phase 3 clinical trials for UC, CD, and Ps, serious infections (n = 99, 2.6%) have been reported commonly during treatment with mirikizumab. When including time-off mirikizumab and the post-treatment follow-up time, serious infections (n = 108, 2.8%) were also reported commonly. 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 7 patients, 5 patients while receiving mirikizumab and 2 patients while off mirikizumab.

All 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 of 65 years or older, body mass index ≥25 kg/m², diabetes mellitus, cardiovascular disease, and/or arterial hypertension. 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.

Characterisation of the risk:

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

Placebo-Controlled Ulcerative colitis Exposures:
In the UC population in the placebo-controlled induction Study AMAN, the frequency of serious infections was similar for patients who received mirikizumab (0.7%) compared to patients who received placebo (0.6%).

In the UC Maintenance Mirikizumab Responders analysis set in the maintenance Study AMBG, serious infections were reported more frequently in patients who received placebo (1.6%) compared with patients who received mirikizumab (0.8%).

All UC Exposures:

In the UC population exposed to mirikizumab in the Phase 2 and Phase 3 clinical trials, (N = 1442), serious infections were reported commonly (n = 33, 2.3%, IR 1.5 per 100 PY) in patients during treatment with mirikizumab and also commonly (n = 39, 2.7%) if including time off mirikizumab. The EAIR of serious infections in this analysis set was 1.5 per 100 PY (95% CI = 1.0 - 2.1). The most frequently reported serious infections during treatment with mirikizumab were pneumonia (n = 5, 0.3%), appendicitis (n = 4, 0.3%), and gastroenteritis (n = 3, 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 pneumonia (n = 6, 0.4%), appendicitis (n = 4, 0.3%), gastroenteritis (n = 3, 0.2%), and sepsis (n = 3, 0.2%). All other serious infections were reported at a frequency of 0.1% or less.

Three patients with UC died from coronavirus or COVID-19 infections:

- One patient died from COVID-19 while receiving mirikizumab on the long-term extension Study I6T-MC-AMAP.
- Two patients died from coronavirus/COVID-19 infection while off mirikizumab:
  - 1 patient with UC who received mirikizumab on the induction Study I6T-MC-AMAN and was receiving placebo on the maintenance Study I6T-MC-AMBG. This death occurred 171 days after the last dose of mirikizumab.
  - 1 patient with UC who received mirikizumab on the induction Study I6T-MC-AMAN and maintenance Study I6T-MC-AMBG, discontinued from Study AMBG due to a malignancy, and withdrew consent after completing the early termination visit. The death due to coronavirus infection was reported in the follow-up information for the malignancy SAE and was reported to have occurred 89 days after the last dose of mirikizumab in the context of a coronavirus infection.

All Mirikizumab Exposures:

In all mirikizumab exposures in Phase 2 and Phase 3 clinical trials for UC, CD, and Ps (N = 3798), serious infections were reported commonly (n = 99, 2.6%, IR 1.3 per 100 PY) in patients during treatment with mirikizumab. The EAIR of serious infections in this analysis set was 1.3 per 100 PY (95% CI = 1.0 - 1.6). The most frequently reported serious infections during treatment with mirikizumab were COVID-19 pneumonia (n = 18, 0.5%), pneumonia (n = 13, 0.3%), and appendicitis (n = 9, 0.2%). All other serious infections were reported at a frequency of 0.1% or less. When including time off mirikizumab, serious infections were reported commonly (n = 108, 2.8%), and the most frequently reported serious infections were COVID-19 pneumonia (n = 33, 0.8%).
pneumonia (n = 18, 0.5%), pneumonia (n = 14, 0.4%), appendicitis (n = 9, 0.2%), and COVID-19 (n = 7, 0.2%). All other serious infections were reported at a frequency of 0.1% or less. In addition to the deaths of patients with UC described above, 4 patients with Ps died from COVID-19 infection or sequelae of this infection while receiving mirikizumab in the long-term extension Study I6T-MC-AMAH.

Blinded Phase 3 CD Study:

One death due to a serious infection with sepsis was reported in a patient with CD who received blinded study drug on the ongoing Study I6T-MC-AMAM and died during the post-treatment follow-up period, 144 days after the last dose of blinded study drug.

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.

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 will raise awareness regarding this risk, aimed for similar outcomes in the post-marketing phase. With the availability of COVID-19 vaccinations and medications, it is expected that the frequency of severe COVID-19 infections and/or sequelae may decrease and/or outcomes may improve.

The label will include a contraindication for patients with active TB and will state that 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. It will also state that patients receiving mirikizumab should be monitored for signs and symptoms of active TB during and after treatment. Additionally, the label will warn 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.

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 Ps, UC, and CD treatment groups, including 3798 patients (7801.3 PYE) in UC 1442 patients (2250.9 PYE), and the EAIR of serious infections in mirikizumab-treated patients of 1.3 per 100 PYE (1.5 per 100 PY in UC). Serious infections were reported commonly in both datasets, and the majority
recovered without sequelae or adverse clinical outcomes. The most frequently reported serious infections in mirikizumab-treated patients across all indications were COVID-19 pneumonia, pneumonia, and appendicitis, and in UC patients specifically, pneumonia, appendicitis, and gastroenteritis. Across the treatment groups, 10 patients 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.

Patients with UC are at risk for systemic rheumatoid disease and may, therefore, be at an increased risk of infection due to the underlying disease and/or prevalent use of concomitant immunosuppressive therapy. Given that an association between immunomodulatory 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:**

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

**Important Potential Risk 2: Severe Liver Injury**

**Potential mechanisms:**

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

**Evidence source(s) and strength of evidence:**

For the UC population exposed to mirikizumab in the Phase 2 and Phase 3 clinical trials, elevated ALT ≥5xULN and ≥10xULN were reported by 0.4% and 0.1% of patients in the mirikizumab treatment group respectively. Elevated AST ≥5xULN and ≥10xULN were reported by 0.7% and 0.1% of patients in the mirikizumab treatment group, respectively.

For all mirikizumab exposures in Phase 2 and Phase 3 clinical trials for UC, CD, and Ps, elevated ALT and AST ≥10xULN was reported for each analyte in 0.1% of mirikizumab-treated patients.

Most of these liver enzyme elevations/increases were considered mild to moderate in severity and 3 patients with Ps had AST and ALT elevations that were reported as serious. None were associated with an adverse clinical outcome. Overall, 0.32% of patients 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 patient with UC met Hy’s law criteria with a maximum ALT of 17.9xULN, maximum AST of 9.9xULN, and maximum bilirubin of 2.4xULN. 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 Ulcerative colitis Exposures:

In the placebo-controlled periods of Studies AMAN and AMBG, transaminase elevations were reported in a small number of patients (≤1%), although there were more patients with treatment-emergent maximum elevations in ALT or AST ≥3xULN and ≥5xULN in the UC Maintenance Mirikizumab Responder analysis set.

All Ulcerative colitis Exposures:

For the UC population exposed to mirikizumab in the Phase 2 and Phase 3 clinical trials, 65 patients (4.5%, IR 3.0 per 100 PY) reported at least 1 narrow scope hepatic TEAE, of which 21 were ALT increased and 19 were AST increased. For 1 patient, the hepatic AE of cholecystitis acute was reported as serious. Three patients discontinued mirikizumab due to a hepatic AE, including 2 patients for hepatic enzyme increased and 1 patient for autoimmune hepatitis.

For the UC population, elevations in transaminases were observed in both mirikizumab-treated patients and those who received placebo. The IRs for ALT elevations were lower for mirikizumab-treated patients compared to placebo except for the elevations of ALT ≥10xULN, which occurred only in patients who received mirikizumab. The IRs for AST elevations were higher in the mirikizumab-treated patients than placebo.

**Table SVII.1. Patients Meeting Elevated Hepatic Criteria Maximum Post-Baseline Values (ALT and AST)**

<table>
<thead>
<tr>
<th>Maximum Post-baseline Category, n (%) [IR]</th>
<th>UC Placebo N = 384</th>
<th>All UC Miri N = 1442</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nx = 377 PYE = 197.2</td>
<td>Nx = 1427 PYE = 2250.9</td>
</tr>
<tr>
<td>ALT ≥3xULN</td>
<td>4 (1.1) [2.0]</td>
<td>28 (2.0) [1.2]</td>
</tr>
<tr>
<td>ALT ≥5xULN</td>
<td>2 (0.5) [1.0]</td>
<td>10 (0.7) [0.4]</td>
</tr>
<tr>
<td>ALT ≥10xULN</td>
<td>0</td>
<td>3 (0.2) [0.1]</td>
</tr>
<tr>
<td>AST ≥3xULN</td>
<td>2 (0.5) [1.0]</td>
<td>30 (2.1) [1.3]</td>
</tr>
<tr>
<td>AST ≥5xULN</td>
<td>0</td>
<td>15 (1.1) [0.7]</td>
</tr>
<tr>
<td>AST ≥10xULN</td>
<td>0</td>
<td>2 (0.1) [0.1]</td>
</tr>
</tbody>
</table>

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; IR = incidence rate; miri = mirikizumab; N = number of participants in the safety analysis set; n = number of participants in specified category; Nx = number of participants in the baseline category and that have at least 1 postbaseline measurement; PYE = patient years of exposure; UC= ulcerative colitis; ULN = upper limit of normal.
All Mirikizumab Exposures:

For all mirikizumab exposures in Phase 2 and Phase 3 clinical trials for UC, CD, and Ps, 256 patients (6.7%, IR 3.4 per 100 PY) reported at least 1 narrow scope treatment emergent hepatic AE, and 8 patients reported a serious hepatic AE, including 7 patients with Ps and 1 patient with UC (referenced above). Fourteen patients discontinued mirikizumab due to a hepatic AE.

For all mirikizumab exposures in Phase 2 and Phase 3 clinical trials for UC, CD, and Ps, elevations in transaminases were observed in both mirikizumab-treated patients and those who received placebo. The IRs for ALT elevations were lower for mirikizumab-treated patients compared to placebo except for the ≥10xULN elevations, which occurred only in patients who received mirikizumab. The IRs for AST elevations were similar for mirikizumab-treated patients and placebo except for the ≥10xULN elevations, which occurred only in patients who received mirikizumab.

Table SVII.2 Patients Meeting Elevated Hepatic Criteria Maximum Post-Baseline Values (ALT and AST)

<table>
<thead>
<tr>
<th>Maximum Post-baseline Category, n (%) [IR]</th>
<th>All Placebo</th>
<th>All Miri</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 719</td>
<td>N = 3798</td>
</tr>
<tr>
<td></td>
<td>Nx = 711</td>
<td>Nx = 3773</td>
</tr>
<tr>
<td></td>
<td>PYE = 289.6</td>
<td>PYE = 7801.3</td>
</tr>
<tr>
<td>ALT ≥3xULN</td>
<td>9 (1.3)</td>
<td>115 (3.0)</td>
</tr>
<tr>
<td></td>
<td>[3.0]</td>
<td>[1.5]</td>
</tr>
<tr>
<td>ALT ≥5xULN</td>
<td>5 (0.7)</td>
<td>24 (0.6)</td>
</tr>
<tr>
<td></td>
<td>[1.7]</td>
<td>[0.3]</td>
</tr>
<tr>
<td>ALT ≥10xULN</td>
<td>0</td>
<td>8 (0.2)</td>
</tr>
<tr>
<td></td>
<td>[0.1]</td>
<td>[0.1]</td>
</tr>
<tr>
<td>AST ≥3xULN</td>
<td>4 (0.6)</td>
<td>104 (2.8)</td>
</tr>
<tr>
<td></td>
<td>[1.3]</td>
<td>[1.3]</td>
</tr>
<tr>
<td>AST ≥5xULN</td>
<td>1 (0.1)</td>
<td>42 (1.1)</td>
</tr>
<tr>
<td></td>
<td>[0.3]</td>
<td>[0.5]</td>
</tr>
<tr>
<td>AST ≥10xULN</td>
<td>0</td>
<td>9 (0.2)</td>
</tr>
<tr>
<td></td>
<td>[0.1]</td>
<td>[0.1]</td>
</tr>
</tbody>
</table>

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; IR =incidence rate; miri = mirikizumab; N = number of participants in the safety analysis set; n = number of participants in specified category; Nx = number of participants in the baseline category and that have at least 1 postbaseline measurement; PYE = patient years of exposure; ULN = upper limit of normal.

Risk factors and risk groups:

In the UC, CD, and Ps 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 UC programme, no specific risk factors have been identified.

Preventability:
As no risk groups or risk factors have been identified, elevations in liver enzymes are unlikely to be preventable. Early detection of liver enzyme elevations and application of an appropriate intervention may help to prevent outcomes from becoming serious, therefore, the proposed monitoring will allow early detection of changes that may later increase and/or require intervention.

ALT increased and AST increased are ADRs for mirikizumab, and the warning and precaution language will advise that if increases in ALT or AST are observed and drug-associated liver injury is suspected, mirikizumab should be discontinued until this diagnosis is excluded.

Impact on the risk-benefit balance of the product:
A majority of hepatic AEs reported in all mirikizumab exposures in Phase 2 and Phase 3 clinical trials for UC, along with the data from all mirikizumab exposures including patients with CD and Ps, 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 and the one case meeting Hy’s law criteria had rapid resolution of liver enzymes upon discontinuation of mirikizumab. Across the mirikizumab programme, a total of 14 patients discontinued mirikizumab due to a hepatic AE. Other than 1 patient with UC who discontinued due to AIH and 1 patient with Ps who discontinued due to Hepatitis B DNA positive assay, all other discontinuations were due to increased hepatic enzyme/liver function tests (n = 12). Based on the available clinical data, the current impact on the risk-benefit balance of mirikizumab is considered low. Labelling is expected to inform prescribers of the potential risk of severe liver injury.

Public health impact:
Mirikizumab will be indicated for a clearly defined subset of the population with moderately to severely active UC, 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 to be associated with an increased risk of malignancy (Jussila et al. 2013; Manninen et al. 2013; Hovde et al. 2017), which may be confounded by behavioral risk factors and current use of certain therapies to treat the disease (for example, thiopurine use).

In participants with UC who received mirikizumab, the frequency of malignancies and NMSC was low, and the data suggest there was no increase in the frequency of malignancy events with increasing duration of mirikizumab treatment. The IR of malignancies in this population (0.8 per 100 PYs) was consistent with the IRs reported in the general population of patients with UC in observational studies (Biancone et al. 2016, Taborelli et al. 2020) and did not suggest an increased risk associated with mirikizumab use.

Characterisation of the risk:

Frequency

Among participants with UC in the clinical development programme (N=1442; total PYE=2250.9), 19 participants reported ≥ 1 TE malignancy (0.8 per 100 PYE), which included 14 participants with malignancies excluding NMSC and 5 participants with NMSC.

Across the entire mirikizumab clinical development program, including participants with Ps, UC, and CD (N=3798; total PYE=7801.3), 58 participants reported ≥ 1 TE malignancy (0.7 per 100 PYE), which included 41 participants with malignancies excluding NMSC and 18 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 UC are at a known increased risk for malignancy, which may be additionally confounded by individual behavioral risk factors and concurrent use of certain therapies to treat the disease.

This assessment is based on the clinical profile from the UC clinical trial database, with exposure from 1442 patients (2250.9 PYE). In the UC clinical development programme, malignancy has been reported in 19 participants, with an IR of 0.8 per 100 PYE. 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.

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.

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,” 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 UC treatment population, there was no observed association between mirikizumab treatment and MACE. No cases of MACE were observed in the UC placebo-controlled population. There was a small imbalance of MACE between treatment groups in the placebo-
controlled Ps study population, with the randomisation ratio of mirikizumab to placebo of 6:1 being a contributing factor.

IRs for MACE observed in the All UC 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 (IR=1.1) and Ps (IR=0.4 to 1.5) populations.

Characterisation of the risk:

In participants with UC, adjudicated and confirmed MACE were reported in 5 participants (0.4%, IR=0.2, 95% CI 0.1, 0.5) in the All UC Mirikizumab Exposures Integrated Analysis Set. The IR for adjudicated and confirmed MACE is below published rates for the background population with UC (IR=1.1).

In participants with psoriasis, adjudicated and confirmed MACE were reported in

- 5 participants (0.4%, IR=1.2, CI 0.4, 2.9) in the Ps Induction Placebo-Controlled Integrated Analysis Set. The IR of MACE in this population is within the range of the background IR for patients with moderate-to-severe Ps (IR=0.4 to 1.5).

In all participants treated with mirikizumab, adjudicated and confirmed MACE were reported for

- 26 participants (0.7%, IR=0.3, CI 0.2, 0.5) in the All Mirikizumab Exposures Integrated Analysis Set. This IR of adjudicated and confirmed MACE is below the range of the background IR in the UC population (1.1 IR) and moderate-to-severe Ps 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 Ps.

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 UC 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. Patients with UC are at a known increased risk for cardiovascular disorders. This assessment is based on the clinical profile from the UC clinical trial database, with exposure from 1442 patients (2250.9 PYE). In the UC clinical development programme, 5 participants were confirmed after independent adjudication to have experienced a MACE, with an IR of 0.2 per 100 PYE. The totality of the data, in which few TE MACE were
reported from all participants with UC and Ps and the lack of a conclusive biological mechanism for MACE with IL-23p19 inhibition, do not represent sufficient scientific evidence of a relationship with mirikizumab treatment.

Lilly will monitor reported events of MACE 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,” of which MACE is an objective.

Public health impact:

Given the low incidence of MACE in the range of disease-related background rates and 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.
## Module SVIII - Summary of the Safety Concerns

### Table SVIII.1. Summary of Safety Concerns

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
<th>Important identified risks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important potential risks</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Serious infections</td>
</tr>
<tr>
<td></td>
<td>• Severe liver injury</td>
</tr>
<tr>
<td></td>
<td>• Malignancies</td>
</tr>
<tr>
<td></td>
<td>• MACE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Missing information</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Safety of mirikizumab in pregnant women and lactating women</td>
</tr>
</tbody>
</table>

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 – Infection
- Spontaneous Follow-up Form – Extrapulmonary Tuberculosis
- Spontaneous Follow-up Form – 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
- Spontaneous Follow-up Form – Breast feeding
- Spontaneous Follow-up Form – Hepatic Disorders
- Spontaneous Follow-up Form – Cancer
- Spontaneous Follow-up Form – Cardiac Disorders
- 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 Lilly’s routine signal evaluation processes.

III.2 Additional Pharmacovigilance Activities

Study Short Name and Title:

Observational Secondary Database Cohort Study on Mirikizumab Exposure and Pregnancy.

Rationale and Study Objectives:

Pregnant women were not included in the mirikizumab clinical development programme. However, the indicated population for mirikizumab of patients with UC includes women of childbearing age. Therefore, exposure to mirikizumab during pregnancy may occur during post-marketing. 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, effects pregnancy, and foetal or infant outcomes in humans have not been fully determined. Therefore, the purpose of this study is to determine the pregnancy, and foetal or infant outcomes among pregnant women with a diagnosis of UC who are exposed to mirikizumab.
The pregnancy, maternal and foetal or infant outcomes of interest include:

- Pregnancy outcomes: recognised spontaneous abortions, stillbirths, elective terminations, and preterm delivery
- Foetal or infant outcomes: small for gestational age, and major and minor 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 the limited number of pregnant women with a diagnosis of UC 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 a diagnosis of UC who are exposed to mirikizumab during pregnancy to pregnant women with a diagnosis of UC who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC.

Study Design:

Observational cohort study using secondary data from administrative claims databases in the US.

Study Population:

Pregnant women with a diagnosis of UC.

Milestones:

The proposed milestones are as follows:

| Milestones                  | Anticipated due date
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of data collection</td>
<td>Within 2 years of first regulatory approval</td>
</tr>
<tr>
<td>Study progress report</td>
<td>To be provided with the PSUR†</td>
</tr>
<tr>
<td>Interim report</td>
<td>Approximately 4 years after the start of data collection</td>
</tr>
<tr>
<td>Final study report</td>
<td>31 Dec 2031</td>
</tr>
</tbody>
</table>

Abbreviation: PSUR = periodic safety update report.

*Dates are estimated and will be finalised once appropriate data source and vendor are identified.

†After the start of data collection.

Study Short Name and Title

Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab

Rationale and Study Objectives:

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

The objective of this study is to examine the incidence of severe liver injury, serious infections, including opportunistic infections, malignancies excluding non-melanoma skin cancer (NMSC) and MACE among patients with a diagnosis of UC who are exposed to mirikizumab compared to patients with a diagnosis of UC who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC 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 claims databases in the US.

Study Population:
Adult patients 18 years of age or older with a diagnosis of UC

Milestones:

The proposed milestones are as follows:

<table>
<thead>
<tr>
<th>Milestones</th>
<th>Anticipated due date*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of data collection</td>
<td>Within 2 years of first regulatory approval</td>
</tr>
<tr>
<td>Study progress report</td>
<td>To be provided with the PSUR†</td>
</tr>
<tr>
<td>Interim report</td>
<td>Approximately 7 years after the start of data collection</td>
</tr>
<tr>
<td>Final study report</td>
<td>31 Dec 2037</td>
</tr>
</tbody>
</table>

Abbreviation: PSUR = periodic safety update report.

*Dates are estimated and will be finalised once appropriate data source and vendor are identified.
†After the start of data collection.
### III.3 Summary Table of Additional Pharmacovigilance Activities

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

<table>
<thead>
<tr>
<th>Study (study short name, and title)</th>
<th>Summary of objectives</th>
<th>Safety concerns addressed (list)</th>
<th>Milestones (required by regulators)</th>
<th>Due dates (in DD/Mon/YYYY format)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category 1</strong> - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Category 2</strong> – Imposed mandatory additional pharmacovigilance activities that are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Category 3** - Required additional pharmacovigilance activities | Observational Secondary Database Cohort Study on Mirikizumab Exposure and Pregnancy 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 ulcerative colitis 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 ulcerative colitis who are exposed to mirikizumab during pregnancy to women with ulcerative colitis who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the | Missing information: Use in pregnancy. | 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 (study short name, and title)**  
**Status (planned/ongoing)**  

<table>
<thead>
<tr>
<th>Study</th>
<th>Summary of objectives</th>
<th>Safety concerns addressed (list)</th>
<th>Milestones (required by regulators)</th>
<th>Due dates (in DD/Mon/YYYY format)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab</strong></td>
<td>- To examine the incidence of severe liver injury, serious infections including opportunistic infections, malignancies excluding non-melanoma skin cancer and MACE among patients with ulcerative colitis who are exposed to mirikizumab compared to patients with ulcerative colitis who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of ulcerative colitis, in real world clinical practice in the US.</td>
<td>Important potential risks: Severe liver injury, serious infections, malignancy, and MACE.</td>
<td>Start of data collection</td>
<td>Within 2 years of first regulatory approval</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Study progress report</td>
<td>To be submitted with the PSUR (after the start of data collection)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Interim report</td>
<td>Approximately 7 years after the start of data collection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Final report</td>
<td>31 Dec 2037</td>
</tr>
</tbody>
</table>

Abbreviations: MACE = major adverse cardiovascular event; PSUR = periodic safety update report.  
*Dates are estimated and will be finalised once appropriate data source and vendor are identified.
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

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation activities</th>
</tr>
</thead>
</table>
| 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. You must look out for signs of these conditions while you are using mirikizumab.

- 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
  - fever
  - chills
  - muscle aches
  - cough
  - shortness of breath
  - 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 clinical development programme (including the placebo-controlled and open-label induction and maintenance periods), there have been elevations of ALT to ≥3x upper limit of normal (ULN) (2.0%), ≥5xULN (0.7%) and ≥10xULN (0.2%) and AST to ≥3xULN (2.1%), ≥5xULN (1.1%), and ≥10xULN (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**
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancies</td>
<td>Routine risk communication: None</td>
</tr>
<tr>
<td>MACE</td>
<td>Routine risk communication: None</td>
</tr>
</tbody>
</table>
| 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

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Risk Minimisation Measures</th>
<th>Pharmacovigilance Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious infections</td>
<td>Routine risk minimisation measures:</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection include the following:</td>
</tr>
<tr>
<td></td>
<td>- SmPC Section 4.3 Contraindications</td>
<td>- Spontaneous Follow-up Form - Infection</td>
</tr>
<tr>
<td></td>
<td>- SmPC Section 4.4 Special Warnings and Precautions for Use</td>
<td>- Spontaneous Follow-up Form - Extrapulmonary Tuberculosis</td>
</tr>
<tr>
<td></td>
<td>- PL Section 2</td>
<td>- Spontaneous Follow-up Form - Pulmonary Tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Additional risk minimisation measures: None proposed</td>
<td>Additional pharmacovigilance activities: An Observational Secondary Database Study to Assess the Long-term Safety of Mirikizumab.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- To examine the incidence of severe liver injury, <strong>serious infections</strong> including opportunistic infections, malignancies excluding non-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>melanoma skin cancer (NMSC), and MACE among patients with a diagnosis of UC who are exposed to mirikizumab compared to patients with a diagnosis of UC who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC, in real world clinical practice in the US.</td>
</tr>
<tr>
<td>Severe liver injury</td>
<td>Routine risk minimisation measures:</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection include the following:</td>
</tr>
<tr>
<td></td>
<td>- SmPC Section 4.4 Special Warnings and Precautions for Use</td>
<td>- Spontaneous Follow-up Form - Hepatic Disorders</td>
</tr>
<tr>
<td></td>
<td>- SmPC Section 4.8 Undesirable Effects</td>
<td>Additional pharmacovigilance activities: An Observational Secondary Database Study to Assess the Long-term Safety of Mirikizumab.</td>
</tr>
<tr>
<td></td>
<td>- PL Section 2</td>
<td>- To examine the incidence of <strong>severe liver injury</strong>, serious infections including opportunistic infections, malignancies excluding non-</td>
</tr>
<tr>
<td></td>
<td>Additional risk minimisation measures: None proposed</td>
<td></td>
</tr>
<tr>
<td>Safety Concern</td>
<td>Risk Minimisation Measures</td>
<td>Pharmacovigilance Activities</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------------------</td>
<td>-------------------------------</td>
</tr>
</tbody>
</table>
| Malignancies  | Routine risk minimisation measures: None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection include the following:  
- Spontaneous Follow-up Form - Cancer  
Additional pharmacovigilance activities: An observational secondary database study to assess the long-term safety of mirikizumab.  
- To examine the incidence of severe liver injury, serious infections including opportunistic infections, **malignancies excluding non-melanoma skin cancer (NMSC)**, and MACE among patients with a diagnosis of UC who are exposed to mirikizumab compared to patients with a diagnosis of UC who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC, in real world clinical practice in the US. |
| MACE          | Routine risk minimisation measures: None | 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: An observational secondary database study to assess the long-term safety of mirikizumab. |
<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Risk Minimisation Measures</th>
<th>Pharmacovigilance Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety of mirikizumab in pregnant women and lactating women</td>
<td>Routine risk minimisation measures:</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection include the following:</td>
</tr>
<tr>
<td></td>
<td>- SmPC Section 4.6 Fertility, Pregnancy, and Lactation</td>
<td>- Spontaneous Follow-up Form – Pregnancy Data Collection – Maternal</td>
</tr>
<tr>
<td></td>
<td>- PL Section 2</td>
<td>- Spontaneous Follow-Up Form – Pregnancy Data Collection – Paternal</td>
</tr>
<tr>
<td>Additional risk minimisation measures:</td>
<td>None proposed</td>
<td>- Spontaneous Follow-Up Form – Pregnancy Outcome – Maternal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Spontaneous Follow-Up Form – Pregnancy Outcome – Paternal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Spontaneous Follow-Up Form – Breast Feeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Additional pharmacovigilance activities: An Observational Secondary Database Cohort Study on Mirikizumab Exposure and Pregnancy:</td>
</tr>
<tr>
<td>Safety Concern</td>
<td>Risk Minimisation Measures</td>
<td>Pharmacovigilance Activities</td>
</tr>
<tr>
<td>----------------</td>
<td>-----------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• To monitor the use of mirikizumab among women of childbearing age.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• To determine the incidence of pregnancy and foetal or infant outcomes among pregnant women with ulcerative colitis who are exposed to mirikizumab during pregnancy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If sufficient sample sizes allow to compare the incidence of pregnancy and foetal/infant outcomes of pregnant women with ulcerative colitis who are exposed to mirikizumab during pregnancy to women with ulcerative colitis who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of ulcerative colitis.</td>
</tr>
</tbody>
</table>

Abbreviations: MACE = major adverse cardiac event; NMSC = non-melanoma skin cancer; PL = package leaflet; SmPC = summary of product characteristics; UC = ulcerative colitis.

*Dates are estimated and will be finalised once appropriate data source and vendor are identified.
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).

<table>
<thead>
<tr>
<th>List of important risks and missing information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risks</td>
</tr>
<tr>
<td>Important potential risks</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Missing information</td>
</tr>
</tbody>
</table>

Abbreviation: MACE = major adverse cardiac event.

II.B Summary of Important Risks

Important potential risk: Serious infections

In patients with UC across the Phase 2 and Phase 3 studies, serious infections ($n = 33, 2.3\%$) were reported commonly during treatment with mirikizumab. When including time-off mirikizumab and the post-treatment follow-up period, serious infections ($n = 39, 2.7\%$) were also reported commonly. Although the majority of patients recovered, serious infections due to coronavirus or COVID-19 infections resulted in the deaths of 3 patients with UC, 1 while receiving mirikizumab and 2 while off mirikizumab.

Across all mirikizumab exposures in Phase 2 and Phase 3 clinical trials for UC, CD, and Ps, serious infections ($n = 99, 2.6\%$) have been reported commonly during treatment with mirikizumab. When including time-off mirikizumab and the post-treatment follow-up time, serious infections ($n = 108, 2.8\%$) were also reported commonly. 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 7 patients, 5 patients while receiving mirikizumab and 2 patients while off mirikizumab.

All 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 hospitalization, severe disease, and/or death due to COVID-19 based on one or more of the following criteria: age $\geq 65$ years, BMI $\geq 25\; \text{kg/m}^2$, diabetes mellitus, cardiovascular disease, and/or arterial hypertension. 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 groups and 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

<table>
<thead>
<tr>
<th>Routine risk minimisation measures:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SmPC Section 4.3, Contraindications</td>
</tr>
<tr>
<td>• SmPC Section 4.4, Special Warnings and Precautions for Use</td>
</tr>
<tr>
<td>• PL Section 2</td>
</tr>
</tbody>
</table>

Additional risk minimisation measures: None proposed

### Additional pharmacovigilance activities

- Additional pharmacovigilance activities: Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab.

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 the UC population exposed to mirikizumab in the Phase 2 and Phase 3 clinical trials, elevated ALT $\geq 5x$ULN and $\geq 10x$ULN were reported by 0.4% and 0.1% of patients in the mirikizumab treatment group respectively. Elevated AST $\geq 5x$ULN and $\geq 10x$ULN were reported by 0.7% and 0.1% of patients in the mirikizumab treatment group respectively.

For all mirikizumab exposures in Phase 2 and Phase 3 clinical trials for UC, CD, and Ps, elevated ALT and AST $\geq 10x$ULN was reported for each analyte in 0.1% of mirikizumab-treated patients.

Most of these liver enzyme elevations/increases were considered mild to moderate in severity and 3 patients with Ps had AST and or ALT elevations that were reported as serious. None were associated with an adverse clinical outcome. Overall, 0.34% of patients 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 patient with UC met Hy’s law criteria with a maximum ALT of 17.9xULN, maximum AST of 9.9xULN, and maximum bilirubin of 2.4xULN. This TEAE of “hepatic enzyme increased” was reported as moderate severity and as non-serious. As no alternative aetiology for 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.

#### Risk factors and risk groups

In the UC, CD, and Ps 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 UC 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
<table>
<thead>
<tr>
<th>Additional pharmacovigilance activities</th>
<th>Additional pharmacovigilance activities: Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab. See Section II.C of this summary for an overview of the post-authorisation development plan.</th>
</tr>
</thead>
</table>

### Important potential risk: Malignancies

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>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.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Risk factors and risk groups</th>
<th>No specific risk factors for malignancy in relation to treatment with mirikizumab have been identified.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Risk minimisation measures</th>
<th>None</th>
</tr>
</thead>
</table>

### Important potential risk: MACE

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>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.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Risk factors and risk groups</th>
<th>No specific risk factors for MACE in relation to treatment with mirikizumab have been identified.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Risk minimisation measures</th>
<th>None</th>
</tr>
</thead>
</table>

### Additional pharmacovigilance activities

<table>
<thead>
<tr>
<th>Additional pharmacovigilance activities</th>
<th>Additional pharmacovigilance activities: Observational secondary database study to assess the long-term safety of mirikizumab. See Section II.C of this summary for an overview of the post-authorisation development plan.</th>
</tr>
</thead>
</table>

Approved on 28 Mar 2023 GMT
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; Ps = psoriasis; 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

<table>
<thead>
<tr>
<th>Risk minimisation measures</th>
<th>Routine risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• SmPC Section 4.6, Fertility, Pregnancy, and Lactation</td>
</tr>
<tr>
<td></td>
<td>• PL Section 2</td>
</tr>
</tbody>
</table>

Additional risk minimisation measures: None proposed

<table>
<thead>
<tr>
<th>Additional pharmacovigilance activities</th>
<th>Additional pharmacovigilance activities: Observational Secondary Database Cohort Study on Mirikizumab Exposure and Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>See Section II.C of this summary for an overview of the post-authorisation development plan.</td>
</tr>
</tbody>
</table>

Abbreviation: 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 short name: Observational Secondary Database Cohort Study on Mirikizumab Exposure and Pregnancy.

Purpose of the study: Pregnant women were not included in the mirikizumab clinical development programme. However, the indicated population for mirikizumab of patients with UC includes women of childbearing age. Therefore, exposure to mirikizumab during pregnancy may occur during post-marketing setting. 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, effects on pregnancy and foetal or infant outcomes in humans have not been fully determined. Therefore, the purpose of this study is to determine the pregnancy, and foetal or infant outcomes among pregnant women with a diagnosis of UC who are exposed to mirikizumab.

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

1. Pregnancy outcomes: recognized spontaneous abortions, stillbirths, elective terminations, and preterm delivery
2. Foetal or infant outcomes: small for gestational age, and major and minor 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 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 a diagnosis of UC who are exposed to mirikizumab during pregnancy to pregnant women with a diagnosis of UC.
who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC.

Study short name: Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab.

Purpose of the study: Data from clinical trials demonstrate that mirikizumab is effective in the treatment of patients with moderate to severe UC. However, the long-term safety of mirikizumab exposure in terms of events with a low frequency and/or long latency among patients with ulcerative colitis in routine clinical practice has not been fully characterised.

Study Objectives

The objective of this study is to examine the incidence of severe liver injury, serious infections, including opportunistic infections, malignancies excluding non-melanoma skin cancer (NMSC), and MACE among patients with a diagnosis of UC who are exposed to mirikizumab compared to patients with UC who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC 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

<table>
<thead>
<tr>
<th>Annex</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annex 4 - Specific Adverse Drug Reaction Follow-up Forms</td>
<td>71</td>
</tr>
<tr>
<td>Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)</td>
<td>100</td>
</tr>
</tbody>
</table>
Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

<table>
<thead>
<tr>
<th>Specific Adverse Event Follow-up Form</th>
<th>Event(s) Associated with the Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form #1</td>
<td>Infection</td>
</tr>
<tr>
<td>Form #2</td>
<td>Extrapulmonary Tuberculosis</td>
</tr>
<tr>
<td>Form #3</td>
<td>Pulmonary Tuberculosis</td>
</tr>
<tr>
<td>Form #4</td>
<td>Pregnancy Data Collection - Maternal</td>
</tr>
<tr>
<td>Form #5</td>
<td>Pregnancy Data Collection - Paternal</td>
</tr>
<tr>
<td>Form #6</td>
<td>Pregnancy Outcome - Maternal</td>
</tr>
<tr>
<td>Form #7</td>
<td>Pregnancy Outcome - Paternal</td>
</tr>
<tr>
<td>Form #8</td>
<td>Breastfeeding</td>
</tr>
<tr>
<td>Form #9</td>
<td>Hepatic Disorders</td>
</tr>
<tr>
<td>Form #10</td>
<td>Cancer</td>
</tr>
<tr>
<td>Form #11</td>
<td>Cardiac Disorders</td>
</tr>
<tr>
<td>Form #12</td>
<td>Cerebrovascular Accident</td>
</tr>
</tbody>
</table>
# Spontaneous Follow-up Form

Reported Events: Infection

**Date:**

**Lilly Case #:**

**Information Provided By:**

**Signature/Initials:**

**Fax:**

**Patient’s Name or Initials:**

**Patient’s Birth Date or Age:**

<table>
<thead>
<tr>
<th>Gender:</th>
<th>Race:</th>
<th>Weight:</th>
<th>Height:</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ F ☐ M ☐ Unknown</td>
<td>☐ Caucasian ☐ Asian ☐ Black ☐ Other</td>
<td>☐ lb ☐ kg</td>
<td>☐ in ☐ cm</td>
</tr>
</tbody>
</table>

**Reported Drug:** Mirikizumab

**Lot/Control Number (if available):**

**Indication:**

**Dose:**

**Frequency:**

**Formulation:**

**Route:**

**Start Date:**

**Date when event occurred:**

**Drug D/C:** ☐ No ☐ Yes

**Date D/C:**

**If Discontinued, did the event resolve?** ☐ Yes ☐ No

**Drug Restarted?** ☐ No ☐ Yes

**Date Restarted:**

**If Restarted, did the event occur?** ☐ Yes ☐ No

## 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:**

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Normal Range</th>
<th>Baseline Value</th>
<th>Abnormal Value</th>
<th>Improvement Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td></td>
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<tr>
<td>WBC</td>
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<td>Platelets</td>
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<td>ALT</td>
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<td>AST</td>
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<tr>
<td>Alkaline Phosphatase</td>
<td></td>
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<tr>
<td>Bilirubin</td>
<td></td>
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<tr>
<td>Creatinine</td>
<td></td>
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</tr>
</tbody>
</table>

Page 1 of 2

Please fax to: Lilly (US) Global Patient Safety - (866) 644-1697 DC 4027
Eli Lilly and Company - Global Patient Safety

<table>
<thead>
<tr>
<th>Case Number:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Was this event related to a Lilly drug?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection *</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered</td>
</tr>
</tbody>
</table>

Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

---

Approved on 28 Mar 2023 GMT
Spontaneous Follow-up Form

Reported Events: Extrapulmonary Tuberculosis

Date: ___________________________  Lilly Case #: ___________________________

Information Provided By: ___________________________________________________

Signature/Initials: ___________________________  Fax: ___________________________

Patient’s Name or Initials: ___________________________________________________

Patient’s Birth Date or Age: ___________________________

Gender:  □ F  □ M  □ Unknown

Race:  □ Caucasian  □ Asian  □ Black  □ Other

Weight: ___________________________  kg

Height: ___________________________  cm

Reported Drug: Mirilizumab

Lot/Control Number (if available): ___________________________  Indication: ___________________________

Dose: ___________________________  Frequency: ___________________________  Formulation: ___________________________

Start Date: ___________________________  Dose when event occurred: ___________________________

Drug D/C?  □ No  □ Yes

Drug Restarted?  □ No  □ Yes

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  □ Pyaria  □ 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

Page 1 of 2  Please fax to: Lilly (US) Global Patient Safety - (866) 644-1697 DC 4027
**Eli Lilly and Company - Global Patient Safety**

### Case Number: [ ]

#### Laboratory Results:

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Normal Range</th>
<th>Baseline Value Date</th>
<th>Abnormal Value Date</th>
<th>Improvement Value Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td></td>
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<tr>
<td>Haemoglobin</td>
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<tr>
<td>MBC</td>
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<tr>
<td>Platelets</td>
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<td>Alkaline phosphatase</td>
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<td>Bilirubin</td>
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<tr>
<td>Creatinine</td>
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<td>CSF Cell Count</td>
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<td>CSF Glucose</td>
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<tr>
<td>Urinalysis</td>
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<tr>
<td>Other:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Extrapulmonary Tuberculosis

- [ ] Yes
- [ ] No
- [ ] Unknown

**Event outcome**

- [ ] Recovered
- [ ] Not Recovered
- [ ] Recovering
- [ ] Worsened
- [ ] Unknown
- [ ] Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

---

Approved on 28 Mar 2023 GMT
Spontaneous Follow-up Form

Reported Events: Pulmonary Tuberculosis

Date: ____________________________  Lilly Case #: ____________________________

Information Provided By: ____________________________  Signature/Initials: ____________________________  Fax: ____________________________

Patient’s Name or Initials: ____________________________  Patient’s Birth Date or Age: ____________________________

Gender:  □ F  □ M  □ Unknown  Race:  □ Caucasian  □ Asian  □ Black  □ Other  Weight: ____________________________ lb  Height: ____________________________ in

Reported Drug: Mirikizumab

Lot/Control Number (if available): ____________________________  Indication: ____________________________

Dose: ____________________________  Frequency: ____________________________  Formulation: ____________________________

Start Date: ____________________________  Dose when event occurred: ____________________________  Route: ____________________________

Drug D/C?  □ No  □ Yes  Date D/C: ____________________________

Drug Restarted?  □ No  □ Yes  Date Restarted: ____________________________

If Discontinued, did the event resolve?  □ Yes  □ No

If Restarted, did the event occur?  □ Yes  □ No

---

Pulmonary Tuberculosis

Presenting Symptoms

☐ Cough  ☐ Night sweats  ☐ Headache
☐ Sputum  ☐ Confusion  ☐ Back pain
☐ Weight loss  ☐ Haemoptysis  ☐ 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-g release assay  ☐ From TB endemic area  ☐ BCG immunization  ☐ Treatment with INH
☐ HIV infection  ☐ Autoimmune disorder  ☐ Malignancy  ☐ Cancer chemorx

Other relevant history: ____________________________

Concomitant Medications / Substances

☐ Current alcohol use  ☐ Current smoking  ☐ Drug abuse
☐ Corticosteroid(s) (specify): ____________________________
☐ Immunosuppressant(s) (specify): ____________________________
☐ Other medications: ____________________________

Laboratory Tests / Investigations

Skin test for TB  ☐ Positive  ☐ Negative  ☐ Not Done  ☐ Pending
IFN-g 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

Page 1 of 2  Please fax to: Lilly (US) Global Patient Safety - (866) 644-1697 DC 4027

Approved on 28 Mar 2023 GMT
EU Risk Management Plan (Version 0.4)  

Eli Lilly and Company - Global Patient Safety

Case Number: 

Chest CT

Other studies:

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Normal Range</th>
<th>Baseline Value</th>
<th>Abnormal Value</th>
<th>Improvement Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
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<td>Bilirubin</td>
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<tr>
<td>Creatinine</td>
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</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Was this event related to a Lilly drug?  Pulmonary Tuberculosis

*   □ Yes   □ No   □ Unknown

Event outcome

□ Recovered   □ Not Recovered   □ Recovering   □ Worsened   □ Unknown

□ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:


Page 2 of 2  Please fax to: Lilly (US) Global Patient Safety - (866) 644-1697 DC 4027

Approved on 28 Mar 2023 GMT

LY3074828
Spontaneous Follow-up Form

Reported Events: Pregnancy Data Collection - maternal

Date: ___________________________  Lilly Case #: ___________________________
Information Provided By: ____________________________________________________
Signature/initials: __________________________________________________________
Fax: Lilly (US) Global Patient Safety - (866) 944-1697 DC 4027
Patient’s Name or initials: ___________________________________________________
Patient’s Birth Date or Age: ________________________________________________

Gender: ○ F  ○ M  ○ Unknown
Race: ○ Caucasian  ○ Asian  ○ Other
Weight: _____________________________________________________________
Height: ______________________________________________________________

Reported Drug: Mirikizumab

Lot/Control Number (if available): ___________________________  indication: ___________________________
Dose: ___________________________  Frequency: ___________________________  Formulation: ___________________________
Start Date: ___________________________  Dose when event occurred: ___________________________
Drug D/C: ○ No  ○ Yes  Route: ___________________________
Drug Restarted? ○ No  ○ Yes  Date D/C: ___________________________
                          if Discontinued, did the event resolve? ○ Yes  ○ No
                          Date Restarted: ___________________________
                          if Restarted, did the event occur? ○ Yes  ○ No

Pregnancy Data Collection - 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 (e.g., hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, etc.)

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

Page 1 of 2  Please fax to: Lilly (US) Global Patient Safety - (866) 944-1697 DC 4027
### Medical Professional Responsible for Monitoring Patient’s Pregnancy:

- **Name:**
- **Address:**
- **Phone:**
- **Fax:**

### Medical Professional Responsible for Monitoring the Infant:

- **Name:**
- **Address:**
- **Phone:**
- **Fax:**

### Was this event related to a Lilly drug?

- **Pregnancy Data Collection - Maternal**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Yes</th>
<th>No</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Recovered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Recovered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovering</td>
<td></td>
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<tr>
<td>Worsened</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Event outcome

- Recovered
- Not Recovered
- Recovering
- Worsened
- Unknown

- Recovered with Sequela (Please provide details):

### Please provide rationale for relatedness assessment:

- 

---

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LY3074828
Spontaneous Follow-up Form

Reported Events: Pregnancy Data collection - paternal

<table>
<thead>
<tr>
<th>Date:</th>
<th>Lilly Case #:</th>
<th>*</th>
</tr>
</thead>
</table>
| Information Provided By: | Signature/Initials: | Fax: Lilly (US) Global Patient Safety - (866) 944-1997 DC 4027
| Patient’s Name or Initials: | Patient’s Birth Date or Age: |

<table>
<thead>
<tr>
<th>Gender:</th>
<th>Race:</th>
<th>Weight:</th>
<th>Height:</th>
</tr>
</thead>
<tbody>
<tr>
<td>O F M O Unknown</td>
<td>O Caucasian</td>
<td>O Asian</td>
<td>O Black</td>
</tr>
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</table>

Reported Drug: Mirikizumab

<table>
<thead>
<tr>
<th>Lot/Control Number (if available):</th>
<th>indication:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose:</td>
<td>Frequency:</td>
</tr>
<tr>
<td>Start Date:</td>
<td>Dose when event occurred:</td>
</tr>
<tr>
<td>Drug D/C: O No O Yes</td>
<td>Date D/C:</td>
</tr>
<tr>
<td>Drug Restarted? O No O Yes</td>
<td>Date Restarted:</td>
</tr>
</tbody>
</table>

Pregnancy Data Collection - Paternal

Patient (Father) Details

Name or initials: Date of Birth or Age:

Father’s medical history/risk factors (e.g., hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, etc.)

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.)

<table>
<thead>
<tr>
<th>Birth Date</th>
<th>Male or Female</th>
<th>Birth Weight</th>
<th>Weeks Gestation</th>
<th>Lilly Drug Used</th>
<th>Mother or baby complications?</th>
</tr>
</thead>
<tbody>
<tr>
<td>O M</td>
<td>O F</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Maternal medical history/risk factors (e.g., hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, etc.)

Contraceptive method:

Exposure Period for Lilly Drug Used During Current Pregnancy

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

Paternal Concomitant Medications/Substance (please include prescription, OTC, and herbal)
**Eli Lilly and Company - Global Patient Safety**

**Case Number:**

<table>
<thead>
<tr>
<th>Maternal Concomitant Medications/Substances (please include prescription, OTC and herbal)</th>
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<table>
<thead>
<tr>
<th>Maternal Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the mother experienced any complications during this pregnancy? ○ No ○ Yes</td>
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<tr>
<td>Define complications:</td>
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<table>
<thead>
<tr>
<th>Treatment:</th>
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<tr>
<th>Continuing: ○ No ○ Yes</th>
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<thead>
<tr>
<th>Maternal Testing Performed (i.e., amniocentesis, ultrasound, etc.)</th>
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<table>
<thead>
<tr>
<th>Additional Contact Information</th>
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</thead>
<tbody>
<tr>
<td>Medical professional responsible for monitoring the father:</td>
</tr>
<tr>
<td>Name:</td>
</tr>
<tr>
<td>Address:</td>
</tr>
<tr>
<td>Phone:</td>
</tr>
<tr>
<td>Fax:</td>
</tr>
</tbody>
</table>

| Medical professional responsible for monitoring the mother: |
| Name: |
| Address: |
| Phone: |
| Fax: |

<table>
<thead>
<tr>
<th>Was this event related to a Lilly drug?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy Data collection - paternal *</td>
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<tr>
<td>Yes ○ No ○ Unknown</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Event outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Recovered ○ Not Recovered ○ Recovering ○ Worsened ○ Unknown</td>
</tr>
<tr>
<td>○ Recovered with Sequella (Please provide details):</td>
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</table>

<table>
<thead>
<tr>
<th>Please provide rationale for relatedness assessment:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>
Spontaneous Follow-up Form

Reported Events: Pregnancy outcome - maternal

<table>
<thead>
<tr>
<th>Date:</th>
<th>Lilly Case #:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*</td>
</tr>
</tbody>
</table>

Information Provided By: 
Signature/initials: 
Fax: Lilly (US) Global Patient Safety - (866) 944-1697 DC 4027

Patient’s Name or initials: 
Patient’s Birth Date or Age:

Gender: □ F □ M □ Unknown
Race: □ Caucasian □ Asian □ Black □ Other

Weight: [ ] lb [ ] kg
Height: [ ] in [ ] cm

Reported Drug: Miritizumab

Lot/Control Number (if available): 
Indication: 

Dose: 
Frequency: 
Formulation: 

Start Date: 
Dose when event occurred: 
Route: 

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

Drug Restarted? [ ] No [ ] Yes 
If Restarted, did the event occur? [ ] Yes [ ] No 
Date Restarted: ____________________________ 

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.]

<table>
<thead>
<tr>
<th>Birth Date</th>
<th>Male or Female</th>
<th>Birth Weight</th>
<th>Weeks Gestation</th>
<th>Lilly Drug Used</th>
<th>Mother or baby complications?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Maternal medical history/risk factors [e.g., hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, etc.]

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
### Pregnancy/Fetal Outcome

- [ ] Live birth/full term
- [ ] Premature birth (less than 37 weeks)
- [ ] Spontaneous/missed abortion
- [ ] Fetal death in utero/at/birth
- [ ] Live birth with neonatal death
- [ ] Post-natal death

**Were congenital or chromosomal abnormalities detected?**

- [ ] No
- [ ] Yes

Please define:

### Neonatal/Infant Data

<table>
<thead>
<tr>
<th>Infant name or initials:</th>
<th>EDC (Due Date):</th>
<th>Date of Delivery:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Gestational age:***

**Gender:**

- [ ] Undetermined/unknown
- [ ] Male
- [ ] Female

**Apgar scores: at 1 minute**

**at 5 minutes**

**Weight:**

- [ ] grams
- [ ] pounds

**Length:**

- [ ] inches
- [ ] cm

**Infant's overall healthy status?**

### Infant Adverse Events/Complications

Did the infant experience any problems while breastfeeding?  

- [ ] No
- [ ] Yes

Please describe:

### Treatment

**Continuing:**

- [ ] No
- [ ] Yes

**Infant's overall health status:**

### Additional Contact Information

- Medical professional responsible for monitoring patient's pregnancy:
  - [ ] Name:
  - [ ] Address:
  - [ ] Phone:
  - [ ] Fax:

- Medical professional responsible for monitoring the infant:
  - [ ] Name:
  - [ ] Address:
  - [ ] Phone:
  - [ ] Fax:

### Was this event related to a Lilly drug?

**Pregnancy outcome - maternal**

- [ ] *
- [ ] Yes
- [ ] No
- [ ] Unknown

**Event outcome**

- [ ] Recovered
- [ ] Not Recovered
- [ ] Recovering
- [ ] Worsened
- [ ] Unknown

**Recovered with Sequella (Please provide details):**

---

**Page 2 of 3**

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Approved on 28 Mar 2023 GMT
Please provide rationale for relatedness assessment:
Spontaneous Follow-up Form

Reported Events: Pregnancy Outcome - paternal

Date: ______________________  Lilly Case #: ______________________

Information Provided By: ______________________  Fax: ______________________

Signature/Initials: ______________________  Patient's Name or Initials: ______________________

Patient's Birth Date or Age: ______________________

Gender:  ○ F  ○ M  ○ Unknown

Race: ○ Caucasian  ○ Asian  ○ Black  ○ Other

Weight: ______________________  Height: ______________________

In:  Kg  cm

Reported Drug: Mirikizumab

Lot/Control Number (if available): ______________________  Indication: ______________________

Dose: ______________________  Frequency: ______________________  Formulation: ______________________

Start Date: ______________________  Dose when event occurred: ______________________  Route: ______________________

Drug D/C? ○ No  ○ Yes

Drug Restarted? ○ No  ○ Yes

Date D/C: ______________________  If Discontinued, did the event resolve? ○ Yes  ○ No

Date Restarted: ______________________  If Restarted, did the event occur? ○ Yes  ○ No

Pregnancy Outcome Paternal

Patient (Father) Details

Name or initials: ______________________  Date of Birth or Age: ______________________

Father's medical history/risk factors (e.g., hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, etc.): ______________________

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 (e.g., hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, etc.): ______________________

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): ______________________

Page 1 of 3  Please fax to: Lilly (US) Global Patient Safety - (866) 644-1697 DC 4027

Approved on 28 Mar 2023 GMT
### Maternal Concomitant Medications/Substances

<table>
<thead>
<tr>
<th>Please include prescription, OTC and herbal</th>
</tr>
</thead>
</table>

### Maternal Complications

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

Define complications:

### Treatment:

Continuing:  
☐ No  ☐ Yes

### Maternal Testing Performed (i.e., amniocentesis, ultrasound, etc.)

### 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

Were congenital or chromosomal abnormalities detected?  
☐ 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:**
- **Weight:**  
  - ☐ grams  
  - ☐ pounds
- **Length:**  
  - ☐ cm  
  - ☐ inches

- Infant's overall health status:

### Infant Adverse Events/Complications

Did the infant experience any problems while breastfeeding?  
☐ No  ☐ Yes

Please describe:

### Treatment:

Continuing:  
☐ No  ☐ Yes

Infant's overall health status:

### Additional Contact Information

- **Medical professional responsible for monitoring the father:**
  - **Name:**
  - **Address:**
  - **Phone:**
  - **Fax:**

- **Medical professional responsible for monitoring the mother:**
  - **Name:**
  - **Address:**
  - **Phone:**
  - **Fax:**

### Was this event related to a Lilly drug?

* ☐ Yes  ☐ No  ☐ Unknown

### Pregnancy Outcome - paternal

- Event outcome:
  - ☐ Recovered  
  - ☐ Not Recovered  
  - ☐ Recovering  
  - ☐ Worsened  
  - ☐ Unknown
  - ☐ Recovered with Sequellae (Please provide details):
Spontaneous Follow-up Form

Reported Events: Breastfeeding

Date: ___________________________  Lilly Case #: ___________________________

Information Provided By: ___________________________  Signature/initials: ___________________________

Fax: Lilly (US) Global Patient Safety - (866) 944-1997 DC 4027

Patient’s Name or Initials: ___________________________  Patient’s Birth Date or Age: ___________________________

<table>
<thead>
<tr>
<th>Gender:</th>
<th>Race:</th>
<th>Weight:</th>
<th>Height:</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ F  ☐ M  ☐ Unknown</td>
<td>☐ Caucasian  ☐ Asian  ☐ Black  ☐ Other</td>
<td>☐ kg  ☐ in</td>
<td></td>
</tr>
</tbody>
</table>

Reported Drug: Minkizumab

Lot/Control Number (if available): ___________________________  Indication: ___________________________

Dose: ___________________________  Frequency: ___________________________

Start Date: ___________________________  Formulation: ___________________________

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

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

Breast Feeding

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 breastfeeding and any complications.)

<table>
<thead>
<tr>
<th>Birth Date</th>
<th>Male or Female</th>
<th>Birth Weight</th>
<th>Weeks Gestation</th>
<th>Lilly Drug Used</th>
<th>Mother or baby complications?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>☐ M ☐ F</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Maternal Medical history/risk factors [e.g., hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, etc.]

Contraceptive method: ___________________________

Maternal Lilly Drug Information

Drug name: ___________________________  Date of first use: __/__/____

Infant’s age at first use: ___________________________  Date of last use: __/__/____

Infant’s age at last use: ___________________________

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

Breast Feeding Information

Date the breast feeding started: __/__/____  Date breast feeding stopped: __/__/____

Breast feeding continued? ☐ 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:**

### Additional Contact Information

**Medical professional responsible for monitoring the mother:**
- **Name:**
- **Address:**
- **Phone:**
- **Fax:**

**Medical professional responsible for monitoring the infant:**
- **Name:**
- **Address:**
- **Phone:**
- **Fax:**

### Was this event related to a Lilly drug?

**Breastfeeding**

* [ ] Yes
* [ ] No
* [ ] Unknown

**Event outcome**

- [ ] Recovered
- [ ] Not Recovered
- [ ] Recovering
- [ ] Worsened
- [ ] Unknown

- [ ] Recovered with Sequella (Please provide details):

**Please provide rationale for relatedness assessment:**

---

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LY3074828

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**Spontaneous Follow-up Form**

Reported Events: Hepatic Disorders

<table>
<thead>
<tr>
<th>Date:</th>
<th>Lilly Case #:</th>
<th>Information Provided By:</th>
<th>Signature/Initials:</th>
<th>Fax:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient's Name or Initials:</th>
<th>Patient's Birth Date or Age:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender:</th>
<th>Race:</th>
<th>Weight:</th>
<th>Height:</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ F</td>
<td>☐ Caucasian</td>
<td>☐ lb</td>
<td>☐ in</td>
</tr>
<tr>
<td>☐ M</td>
<td>☐ Asian</td>
<td>☐ kg</td>
<td>☐ cm</td>
</tr>
<tr>
<td>☐ Unknown</td>
<td>☐ Black</td>
<td>☐ Other</td>
<td></td>
</tr>
</tbody>
</table>

Reported Drug: Mirikiuzumab

<table>
<thead>
<tr>
<th>Lot/Control Number (if available):</th>
<th>Indication:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Dose:</th>
<th>Frequency:</th>
<th>Formulation:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Start Date:</th>
<th>Dose when event occurred:</th>
<th>Route:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug D/C:</th>
<th>Date D/C:</th>
<th>if Discontinued, did the event resolve?</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ No</td>
<td></td>
<td>☐ Yes ☐ No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Restarted?</th>
<th>Date Restarted:</th>
<th>if Restarted, did the event occur?</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ No</td>
<td></td>
<td>☐ Yes ☐ No</td>
</tr>
</tbody>
</table>

### Hepatic Disorders

**Primary diagnosis for the reported event(s):**

Hospitalization for this event? ☐ Yes ☐ No

**Presenting Signs/Symptoms**

- ☐ Fever
- ☐ Jaundice
- ☐ Abdominal Pain
- ☐ Rash
- ☐ Edema
- ☐ Ascites
- ☐ Joint Effusions
- ☐ Nausea
- ☐ Palmar Erythema
- ☐ Urticaria
- ☐ Confusion
- ☐ Asterixis
- ☐ Arthritis
- ☐ Other:

**Concurrent Events and Disease(s)**

- ☐ Sepsis
- ☐ Kidney Failure
- ☐ Bleeding
- ☐ Hypotension

**Concurrent Disease(s)**

- ☐ HIV
- ☐ Cor Pulmonale
- ☐ Malignancy
- ☐ Tuberculosis
- ☐ Autoimmune disease
- ☐ Inflammatory bowel disease
- ☐ Congestive heart failure
- ☐ Diabetes
- ☐ Other:

**Relevant Past Medical History**

- ☐ None
- ☐ Liver toxin exposure
- ☐ Budd-Chiari syndrome
- ☐ Hepatitis A
- ☐ Cirrhosis Child Pugh B or C
- ☐ Hepatic encephalopathy

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Case Number: .

- Hepatitis C
- Autoimmune hepatitis
- Hepatorenal syndrome
- Gall bladder disease
- Hyperbilirubinemia/jaundice
- Portal Hypertension
- Fatty liver
- Abnormal liver laboratory results
- Other: ____________________________________________________________________

Concomitant Meds/Substances (include prescription, OTC and herbal):
- Current Alcohol
- Current Tobacco
- Current Cocaine/Methamphetamine
- Past Alcohol
- Past Tobacco
- Past Cocaine/Methamphetamine
- Other: ____________________________________________________________________

<table>
<thead>
<tr>
<th>Relevant Laboratory Tests</th>
<th>Normal Range for Your Institution</th>
<th>Baseline Value for Patient</th>
<th>Abnormal Value</th>
<th>Improvement Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>Date</td>
<td>Date</td>
<td>Date</td>
<td></td>
</tr>
<tr>
<td>AST (SGOT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct Bilirubin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alk. Phos.</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>GGT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT:INR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ammonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKP</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet Count</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Serologic Studies (check positive)
- Anti-nuclear Antibody (ANA)
- Anti-liver Kidney Microsomal (anti-LKM)
- Anti-smooth Muscle Antibody (ASMA)
- Cytomegalovirus (CMV) Antibody (anti-CMV)
- Epstein Barr (EBV) Serology
- Other: ____________________________________________________________________

<table>
<thead>
<tr>
<th>Other Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Biopsy</td>
<td></td>
</tr>
<tr>
<td>Hepatic Ultrasound</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td></td>
</tr>
<tr>
<td>CT Scan</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

Treatment provided (please describe)

Was this event related to a Lilly drug?

Page 2 of 3 Please fax to: Lilly (US) Global Patient Safety - (866) 644-1697 DC 4027

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### Event outcome

- [ ] Recovered
- [ ] Not Recovered
- [ ] Recovering
- [ ] Worsened
- [ ] Unknown

- [ ] Recovered with Sequella (Please provide details):

### Please provide rationale for relatedness assessment:

---

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Spontaneous Follow-up Form

Reported Events: Cancer

Date: 
Information Provided By: 
Signature/Initials: 
Fax: Lilly (US) Global Patient Safety - (866) 844-1697 DC 4027

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

<table>
<thead>
<tr>
<th>Gender</th>
<th>Race</th>
<th>Weight</th>
<th>Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ F</td>
<td>☐ Caucasian</td>
<td>☐ lb</td>
<td>☐ cm</td>
</tr>
<tr>
<td>☐ M</td>
<td>☐ Black</td>
<td>☐ kg</td>
<td></td>
</tr>
<tr>
<td>☐ Unknown</td>
<td>☐ Other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reported Drug: Mirikizumab

Lot/Control Number (if available): 
Indication: 
Dose: 
Frequency: 
Formulation: 
Dose when event occurred: 
Route: 
Date D/C: 
If Discontinued, did the event resolve? ☐ Yes ☐ No
Date Restarted: 
If Restarted, did the event occur? ☐ Yes ☐ No

Cancer \ Neoplasm

Primary diagnosis for the reported event(s):

Hospitalization for this event? ☐ Yes ☐ No

☐ 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)

<table>
<thead>
<tr>
<th>Study</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histopathology (please indicate stage/grade, staging classification and tissue source)</td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td></td>
</tr>
<tr>
<td>CAT Scan</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

Medical History/Risk Factors

Page 1 of 2

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Eli Lilly and Company - Global Patient Safety

Case Number: 

- 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):

Treatment provided (please describe):

Was this event related to a Lilly drug?

- Cancer: *  - Yes:  No:  Unknown:  

Event outcome:

- Recovered:  - Not Recovered:  - Recovering:  - Worsened:  - Unknown:  

- Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Approved on 28 Mar 2023 GMT
Spontaneous Follow-up Form

Reported Events: Cardiac Disorders

Date: ___________________________  Lilly Case #: ___________________________

Information Provided By: ___________________________  
Signature/Initials: ___________________________  Fax: ___________________________

Patient’s Name or Initials: ___________________________  Patient’s Birth Date or Age: ___________________________

Gender: 
☐ F  ☐ M  ☐ Unknown

Race: 
☐ Caucasian  ☐ Asian  ☐ Black  ☐ Other

Weight: ___________________________  Height: ___________________________  

Reported Drug: Milikizumab

Lot/Control Number (if available): ___________________________  
Indication: ___________________________

Dose: ___________________________  Frequency: ___________________________  
Formulation: ___________________________

Start Date: ___________________________  Dose when event occurred: ___________________________

Drug D/C?  ☐ No  ☐ Yes

Drug Restarted?  ☐ No  ☐ Yes

Cardiac Disorders

Primary diagnosis for the reported event(s)
☐ Chest Pain/Angina  ☐ Myocardial Infarction  ☐ Arrhythmia  ☐ Other - please describe: ___________________________

Hospitalization for this event?  ☐ Yes  ☐ No

Presenting Signs/Symptoms

☐ Heart Rate: ___________________________  ☐ Blood Pressure: ___________________________

☐ Palpitations

☐ Syncope

☐ Cardiac exam:

☐ Pulmonary exam:

☐ Other (please specify): ___________________________

Relevant Medical History (please specify if needed)

☐ Atrial Arrhythmia

☐ Congenital Heart Abnormalities

☐ Atrioventricular Conduction Disorders

☐ Hypertension

☐ Cardiac Disease

☐ Pulmonary Embolism

☐ Cardiovascular Infection

☐ Psychiatric/Emotional Disorders

☐ Pulmonary Disease

☐ Syncope

☐ Metabolic Disorders

☐ Dizziness

☐ Pericarditis

☐ Substance Abuse

☐ Poor Compliance with BP/Cardiac Meds

Page 1 of 3  Please fax to: Lilly (US) Global Patient Safety - (866) 644-1697 DC 4027

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<table>
<thead>
<tr>
<th>Relevant Laboratory Tests</th>
<th>Normal Range for Your Institution</th>
<th>Baseline Value for Patient</th>
<th>Abnormal Value</th>
<th>Improvement Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Enzyme (Please specify):</td>
<td>Date:</td>
<td>Date:</td>
<td>Date:</td>
<td></td>
</tr>
<tr>
<td>Serum Potassium</td>
<td></td>
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<td></td>
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<tr>
<td>Serum Calcium</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>pO2</td>
<td></td>
<td></td>
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<tr>
<td>O2 Saturation</td>
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<table>
<thead>
<tr>
<th>Other Diagnostic Tests</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>EKG (Q waves)/EKG (QTc Interval)</td>
<td></td>
</tr>
<tr>
<td>Myocardial Scan</td>
<td></td>
</tr>
<tr>
<td>Echocardiogram (ECHOCG)</td>
<td></td>
</tr>
<tr>
<td>Coronary Angiography</td>
<td></td>
</tr>
<tr>
<td>Exercise Stress Test</td>
<td></td>
</tr>
<tr>
<td>QT Interval (milliseconds)</td>
<td></td>
</tr>
<tr>
<td>QTc (Corrected Value)</td>
<td></td>
</tr>
<tr>
<td>How was QT interval measured?</td>
<td>○ Machine ○ Manually ○ Other</td>
</tr>
<tr>
<td>QT correction formula</td>
<td>○ Bazett ○ Frederic ○ Other</td>
</tr>
<tr>
<td>Other:</td>
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</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardioversion/Defibrillation</td>
<td>○ Treatment not required</td>
</tr>
<tr>
<td>Medication (please specify):</td>
<td>○ Ablation</td>
</tr>
<tr>
<td>Other (please specify):</td>
<td></td>
</tr>
</tbody>
</table>

Was this event related to a Lilly drug?

Page 2 of 3

Please fax to: Lilly (US) Global Patient Safety - (866) 644-1697 DC 4027

Approved on 28 Mar 2023 GMT
### Event outcome

<table>
<thead>
<tr>
<th></th>
<th>Recovered</th>
<th>Not Recovered</th>
<th>Recovering</th>
<th>Worsened</th>
<th>Unknown</th>
</tr>
</thead>
</table>

☐ Recovered with Sequela (Please provide details):

---

Please provide rationale for relatedness assessment:

---
Spontaneous Follow-up Form

Reported Events: Cerebrovascular Accident

Date: ___________________________  Lilly Case #: ___________________________
Information Provided By: ______________________________________________________
Signature/Initials: ___________________________  Fax: ___________________________
Patient’s Name or Initials: ______________________________________________________
Patient’s Birth Date or Age: ____________________________________________________

<table>
<thead>
<tr>
<th>Gender:</th>
<th>Race:</th>
<th>Weight:</th>
<th>Height:</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ F</td>
<td>☐ Caucasian</td>
<td>☐ lb</td>
<td>☐ cm</td>
</tr>
<tr>
<td>☐ M</td>
<td>☐ Asian</td>
<td>☐ kg</td>
<td></td>
</tr>
<tr>
<td>☐ Unknown</td>
<td>☐ Black</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>☐ Other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reported Drug: Mirikizumab

Lot/Control Number (if available): ___________________________  Indication: ___________________________
Dose: ___________________________  Frequency: ___________________________  Formulation: ___________________________
Start Date: ___________________________  Dose when event occurred: ___________________________
Drug D/C? ☐ No ☐ Yes  Route: ___________________________
Drug Restarted? ☐ No ☐ Yes  Date D/C: ___________________________
If Discontinued, did the event resolve? ☐ Yes ☐ No  Date Restarted: ___________________________
If Restarted, did the event occur? ☐ Yes ☐ No

Cerebrovascular Accident

Primary Diagnosis for the reported event(s):

Hospitalization for this event? ☐ Yes ☐ No

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
☐ Smoking
☐ Myocardial infarction

☐ Atrial fibrillation  ☐ Head trauma
☐ Hypertension  ☐ Prior stroke
☐ Hyperlipidemia  ☐ Other (please specify):

Relevant Laboratory Tests

<table>
<thead>
<tr>
<th>Normal range for your institution</th>
<th>Baseline value for patient</th>
<th>Abnormal value</th>
<th>Improvement value</th>
</tr>
</thead>
</table>

Page 1 of 2  Please fax to: Lilly (US) Global Patient Safety - (866) 644-1697 DC 4027

Approved on 28 Mar 2023 GMT
### EU Risk Management Plan (Version 0.4)  

#### Case Number:  

<table>
<thead>
<tr>
<th>Test</th>
<th>Date:</th>
<th>Date:</th>
<th>Date:</th>
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</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
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</tr>
<tr>
<td>WBC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet Count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aPTT</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Thrombin Time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Other:</td>
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</table>

**Other Tests**

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
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<tr>
<td>MRI</td>
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</tr>
<tr>
<td>Angiography</td>
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</tr>
<tr>
<td>EEG</td>
<td></td>
</tr>
<tr>
<td>Other:</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment**

- Support and organization
- Thrombolytic agent
- Ablation
- Antithrombotic agent
- Anticoagulant
- Other: __________

**Was this event related to a Lilly drug?**

Cerebrovascular Accident *  

- Yes  
- No  
- Unknown

**Event outcome**

- Recovered  
- Not Recovered  
- Recovering  
- Worsened  
- Unknown

- Recovered with Sequella (Please provide details):

---

Please provide rationale for relatedness assessment:

---

Approved on 28 Mar 2023 GMT
Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Not applicable.