EU Risk Management Plan for

Ebglyss 250 mg solution for injection (Lebrikizumab)

RMP version to be assessed as part of this application:

RMP Version number:	1.0
Data lock point for this RMP:	06-Jun-2022
Date of final sign off:	27-Sep-2023

QPPV name:

Gemma Jiménez Sesé

QPPV oversight declaration:

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

Table of Contents

List of Tables

List of Abbreviations

Term	Definition
AD	atopic dermatitis
AD ALL LEB	Atopic Dermatitis All Lebrikizumab Exposure Analysis Set
AD ALL PC Weeks 0 to 16	Atopic Dermatitis Induction Period Placebo-Controlled Integrated Analysis Set
CI	confidence interval
COPD	chronic obstructive pulmonary disease
HR	hazard ratio
IPF	idiopathic pulmonary fibrosis
ISR	injection-site reactions
JAK	Janus kinase
MACE	major adverse cardiovascular event
NMSC	non-melanoma skin cancer
OR	odds ratio
PL	Package leaflet
PY	patient-years
SMPC	Summary of product characteristics
Q2W	every 2 weeks
Q4W	every 4 weeks
RHL	refractory Hodgkin's lymphoma
RMP	risk management plan
TCS	topical corticosteroids

Part I: Product(s) Overview

Table Part I.1. Product Overview

Active substance(s) (INN or common name)	Lebrikizumab
Pharmacotherapeutic group(s) (ATC Code)	Not available
Marketing Authorisation <Holder> <Applicant>	Almirall S.A.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Ebglyss 250 mg solution for injection in pre-filled syringe Ebglyss 250 mg solution for injection in pre-filled pen
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Lebrikizumab is a recombinant antibody produced in Chinese hamster ovary cells. It consists of 2 heavy chains (445 amino acid residues each) and 2 light chains (218 amino acid residues each) with inter- and intra-chain disulfide bonds that are typical of IgG4 antibodies.
	Summary of mode of action Lebrikizumab is an IgG4 mAb that binds with high affinity and slow off-rate to IL-13 and selectively inhibits IL-13 signalling through the IL-4 receptor alpha/IL-13 receptor alpha 1 pathway, thereby, blocking the downstream effects of IL-13 with high potency. Lebrikizumab-bound IL-13 can still bind IL-13 receptor alpha 2 allowing subsequent internalisation and natural clearance of IL-13. Blockade of IL-13 signalling is expected to be of benefit in diseases where IL-13 is a central cytokine to the disease pathogenesis, such as AD.
	Important information about its composition: Lebrikizumab is a mAb based on the human IgG4 stabilised by a mutated Fc region.
Hyperlink to the Product Information	13-pi
Indication(s) in the EEA	**Current:** Ebglyss is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older with a body weight of at least 40 kg who are candidates for systemic therapy.
Dosage in the EEA	**Current dosage for adult and adolescent patients:** The recommended dose of Ebglyss is 500 mg (two 250 mg injections) at both week 0 and week 2, followed by 250 mg administered subcutaneously every other week up to week 16. Consideration should be given to discontinuing treatment in patients who have shown no clinical response after 16 weeks of treatment. Some patients with initial partial response may further improve with continued treatment every other week up to week 24. Once clinical response is achieved, the recommended maintenance dose of Ebglyss is 250 mg every fourth week.

Pharmaceutical form(s) and strengths	**Current:** Lebrikizumab is supplied as a sterile, liquid formulation for subcutaneous (SC) use. Lebrikizumab is supplied as a 2-mL pre-filled syringe with needle safety device (PFS-NSD) and as a pre-filled pen. The SC formulation contains 125 mg/mL lebrikizumab, histidine, glacial acetic acid, sucrose, polysorbate 20, and water for injection, pH .
Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: AD = atopic dermatitis; ATC = Anatomical Therapeutic Chemical; Fc = fraction crystallisable; IgG4 = immunoglobulin G4; IL = interleukin; INN = International Non-proprietary Names; mAb = monoclonal antibody.

Part II: Safety Specification

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

SI.1 Atopic Dermatitis

SI.1.1 Incidence

Worldwide, the incidence of AD is not well documented. The only identified study reported an incidence of 6.1 per 1000 PY during 2002 to 2006 in the Netherlands (6.5 versus 5.7 for males versus females, respectively) (Verhoeven et al. 2008). The incidence rates for AD in Danish (born from 1997 to 2011) and Swedish (born from 2006 to 2010) children were 21.5 and 30.6 per 1000 PY, respectively (Henriksen et al. 2015).

SI.1.2 Prevalence

The 1-year prevalence of AD among adults is estimated between 2% to 8%in the US, Europe, and Japan (Saeki et al. 2006; Harrop et al. 2007; Diepgen et al. 2016; Barbarot et al. 2018; Sacotte and Silverberg 2018). Approximately, 30% of adult patients with AD have moderate-to-severe disease (Bieber and Straeter 2015). Table SI. presents the prevalence of AD among adults in various countries (Barbarot et al. 2018).

Table SI.1. Prevalence of Atopic Dermatitis

Country/Region	12-month prevalence (%) of AD (with 95% CI) (Barbarot et al. 2018)
US	4.9 (4.6 to 5.2)
Canada	3.5 (3.1 to 3.9)
Japan	2.1 (1.8 to 2.3)
EU	4.4 (4.2 to 4.6)
France	3.6 (3.2 to 4.0)
Germany	2.2 (1.9 to 2.5)
Italy	8.1 (7.5 to 8.6)
Spain	7.2 (6.7 to 7.7)
UK	2.5 (2.2 to 2.8)

Abbreviations: AD = atopic dermatitis; CI = confidence interval.

The 1-year prevalence among individuals aged 12 to 18 years was estimated to be 14.8% based on a multinational, cross-sectional survey study (Silverberg et al. 2021). Within this survey, less than 15% patients with AD reported severe AD. In a survey of 663 256 participants aged 13 to 14 years from 96 countries (Odhiambo et al. 2009), the prevalence ranged from 0.2% (Tibet, China) to 24.6% (Barranquilla, Colombia) for current eczema symptoms, and 0% to 5.8% (Marrakech, Morocco) for symptoms of severe eczema.

SI.1.3 Demographics of the Population in the Indication and Risk Factors for the Disease

Gender

Multiple studies have shown a higher prevalence of AD among females compared with males. For example, in a multinational survey within 8 countries, females had a higher prevalence than males in Canada (4.0% versus 3.0%), France (4.5% versus 2.6%), Germany (2.6% versus 1.8%), Italy (10.0% versus 6.0%), and Spain (9.3% versus 6.1%); whereas the UK, the US, and Japan reported similar prevalence of AD between men and women (Barbarot et al. 2018). Despite this finding of similar prevalence among a Japanese population in the survey study by Barbarot et al., a different clinic-based study in Japan did find a higher prevalence of AD among women (9.3%) compared with men (5.1%) (Saeki et al. 2006). Additionally, 2 large population-based studies of patients with AD in Denmark reported a higher proportion of patients with AD were female (61.8%) compared to male (38.2%) (Vinding et al. 2014; Egeberg et al. 2017a).

Age

The prevalence of AD among adults is well-recognised to be lower than that of children, with AD reported in 15% to 20% of children (Nutten 2015). Even within an adult population, the prevalence of AD decreases with increasing age (Saeki et al. 2006; Wolkewitz et al. 2007; Vinding et al. 2014). For example, in a German study, the prevalence of AD was 5.3%, 3.9%, and 3.4% in adults aged 50 to 59, 60 to 69, and 70 to 74 years, respectively (Wolkewitz et al. 2007).

Race/Ethnicity

There is a paucity of data describing the prevalence of AD in skin of colour populations. As reported by Silverberg and Hanifin 2013, in 1 survey study within the US that asked "During the past 12 months, have you had dermatitis, eczema, or any other red, inflamed skin rash?", the prevalence was

- 7.7% among African American participants
- 10.5% in White participants
- 9.1% in Asian participants, and
- 14.6% in participants reporting "other/multiracial".

One US-based study reported no increased odds of AD among participants who were Black or Hispanic, compared with non-Hispanic White; however, those who were Multiracial, non-Hispanic had increased odds of AD (OR 3.36, 95% CI: 1.31 to 8.58) when compared with non-Hispanic Whites (Chiesa et al. 2019).

Risk factors

Risk factors for the development of AD include a family history of AD as well as family and personal history for other atopic diseases, including asthma, allergic rhinitis, food allergies, and hay fever. Genetic risk factors have been suggested, particularly mutations in the filaggrin gene (Weidinger and Novak 2016). Environmental risk factors for development of AD include western

diets that are high in sugar and poly-unsaturated fatty acids, small family size, high education, and living in urban settings with low exposure to ultraviolet radiation and low humidity (Weidinger and Novak 2016). The presence of multiple comorbid autoimmune diseases shows an increased association with AD. The ORs for those with AD who have 1, 2, and at least 3 autoimmune diseases, are 2.48 (95% CI: 2.26 to 2.71), 3.46 (95% CI: 2.58 to 4.64), and 5.32 (95% CI: 1.87 to 15.18), respectively (Andersen et al. 2017).

SI.1.4 Main Existing Treatment Options

Pharmacologic therapies

Topical corticosteroids

TCS are typically the first-line treatment for moderate-to-severe AD and are effective as a short-term treatment or intermittent long-term treatment. However, continuous long-term use of TCS is not recommended because of the risk of local and systemic side effects (skin atrophy, dyspigmentation, and hypertension).

Topical calcineurin inhibitors

TCIs are considered as an alternative or adjunct treatment, especially where treatment with TCS is either inadvisable or not possible and for steroid-sparing in sensitive areas, such as face and skin folds.

As with TCS, TCI are effective as continuous short-term treatments or intermittent long-term treatment. However, patients with moderate-to-severe AD often need additional therapies to alleviate their most bothersome symptoms.

Topical JAK inhibitor

Ruxolitinib is the first JAK inhibitor approved in the US as topical cream for treatment of mild to moderate AD in the patients aged 12 years and older. Ruxolitinib cream is indicated for short-term and non-continuous chronic treatment (Opzelura package insert, 2022). Therefore, alternative therapeutic options are needed for longer-term, continuous treatment to control chronic skin inflammation in patients with moderate-to-severe AD.

Systemic JAK inhibitors

Baricitinib is an oral small-molecule inhibitor of JAK1, approved in Europe since 2020 for the treatment of moderate-to-severe AD in adults who are candidates for systemic therapy.

Abrocitinib and upadacitinib were approved in 2021 for the treatment of moderate-to-severe AD in adults and adolescents (12 years and older) who are candidates for systemic therapy (Deeks and Duggan 2021, Traidl et al. 2021). Abrocitinib is approved only for adults in the US. Additionally, in the US, use of abrocitinib and upadacitinib is restricted to patients with refractory, moderate-to-severe AD whose disease is not adequately controlled with other systemic drug products, including biologics. Their use is also limited based on increased risk of serious bacterial, fungal, viral, and opportunistic infections leading to hospitalisation or death mortality, malignancies, MACE, and

thrombosis associated with the JAK inhibitor class (Rinvoq package insert, 2022; Cibinqo package insert, 2022).

Other systemic immunosuppressive agents

Other systemic immunosuppressive agents are often used when topical treatment does not achieve sufficient control of AD symptoms. Currently available systemic therapies include non-selective immunosuppressants, such as cyclosporine A, azathioprine, methotrexate, and systemic corticosteroids. Among these, only cyclosporine is approved in some regions for treatment of moderate-to-severe AD and its use is limited to adult patients. Most guidelines recommend systemic corticosteroids for only short-term AD treatment due to severe toxicity and side effects.

Biologic agents

Anti-IL4/IL13 antibody

Dupilumab is an injectable anti-IL-4/IL-13 antibody that was approved as the first biologic for moderate-to-severe AD in 2017. Dupilumab is currently indicated in the US for the treatment of moderate-to-severe AD in adult and paediatric patients aged 6 months and older and in the EU for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older or severe atopic dermatitis in children 6 months to 11 years old.

Anti-IL13 antibody

Tralokinumab is an injectable anti-IL-13 antibody that was approved in 2021 for adult patients with moderate-to-severe AD.

Dupilumab and tralokinumab are effective treatments for some patients while others may show a limited or partial response or even no response at all to treatment. Some patients may show an initial response to treatment and loose response over time.

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

AD is a disease more commonly associated with infancy and childhood; however, it is prevalent among adults as well. Among adult patients with AD, approximately 80% are relapsing-remitting disease from childhood, whereas an estimated 20% are new onset in adulthood (Akdis et al. 2006; Garmhausen et al. 2013). Approximately 30% of the patients with AD have moderate-to-severe disease (Bieber and Straeter 2015). The proportion of AD cases that are severe increases with age (Silverberg and Simpson 2014), resulting in moderate-to-severe AD being more prevalent among adult patients than children. For example, a Danish study on adult patients with AD found that 58.2% of the patients had severe disease (Egeberg et al. 2017a).

Depending on age of onset and disease course, atopy signs and concomitant atopic diseases may differ significantly (Garmhausen et al. 2013). Patients experience significant morbidity from moderate-to-severe AD including skin lesions, intractable pruritus, sleep disturbance, and skin pain (Weidinger and Novak 2016; Vakharia et al. 2017). The persistent itch-scratch cycle can have substantial impacts on physical, emotional, and quality of life measures (Augustin et al. 2022). A

study of adults with moderate-to-severe AD found 21.8% of the patients had clinically relevant anxiety or depression. In severe AD, 100% of the patients had borderline and/or abnormal Hospital Anxiety and Depression Scale scores. Furthermore, patients with AD have an increased risk of bacterial and viral infections, both cutaneous and non-cutaneous, due to defective skin barrier and immunologic dysregulation (Langan et al. 2017). Approximately, 70% of the patients with active AD have colonisation with *Staphylococcus aureus* (Clausen et al. 2017). The prevalence of methicillin-resistant *S. aureus* is significantly higher among patients with moderate-to-severe AD compared to those with mild AD (90% versus 10%) (Ong and Leung 2016). There is a significant association between moderate-to-severe AD and occurrence of depression, anxiety, and suicidal ideation (Ronnstad et al. 2018; Thyssen 2018a).

AD is not a life-threatening condition and until recently, there had been no published research on the impact, if any, on mortality. However, some studies have shown that while the absolute risk of death is very low, there may be a modestly increased risk of death among adult patients with AD compared with a general population (HR = 1.71, 95% CI: 1.20 to 2.44 [Egeberg et al. 2017b] and HR = 1.27, 95% CI: 1.11 to 1.45 [Thyssen et al. 2018b]). The mortality rate among patients with AD was 0.579 per 100 PY (95% CI: 0.511 to 0.656) (Thyssen et al. 2018b).

SI.1.6 Important Co-morbidities

Table SI presents the co-morbidities that occur frequently in patients with AD.

Table SI.2. Important Co-morbidities

Co-morbidity	Prevalence in AD Population (Unless Other Measure Noted)
Depression	AD was associated with double the odds of self-reported clinical depression or clinician-diagnosed depression in adults (OR = 1.99, 95% CI: 1.53 to 2.59) (Davis et al. 2022). The prevalence of depression in patients with AD is reported as follows: Adults • 20.1% (multinational, meta-analysis; Patel et al. 2019) • 21.8% self-reported depression (multinational; Simpson et al. 2016) • 3.0% to 10.1% (EU; Dalgard et al. 2015; Egeberg et al. 2017a) • 17.5% (US; Yu and Silverberg et al. 2015) • 16.1% depressive symptoms of at least 2-weeks duration (Korea; Kim et al. 2015a) • 10.25% self-reported depression (Japan; Arima et al. 2018) Adolescents • 1.3% (South Korea, aged 13 to 18 years; Ahn et al. 2019) • 0.1% (multinational, aged <18 years; Gilaberte et al. 2020)
Anxiety	AD was associated with an increased odds of anxiety in adults (OR = 1.40, 95% CI: 1.12 to 1.75) (Davis et al. 2022). The prevalence of anxiety in patients with AD is reported as follows: Adults

Co-morbidity	Prevalence in AD Population (Unless Other Measure Noted)
	• 21.8% self-reported anxiety (multinational; Simpson et al. 2016) • 1.2% to 17.6% (EU; Dalgard et al. 2015; Egeberg et al. 2017a) • 42.5% self-reported anxiety (US; Whiteley et al. 2016) • 9.8% male patients with AD (Korea; Kim et al. 2015b) • 3.3% self-reported anxiety (Japan; Arima et al. 2018) Adolescents • 1.3% (South Korea, aged 13-18 years; Ahn et al. 2019) • 0.2% anxiety, neuroses (multinational, aged <18 years; Gilaberte et al. 2020)
Suicidal ideation/behaviours	Adults with AD are more likely to have suicidal ideation than adults without AD (OR = 1.71, 95% CI: 1.43 to 2.03) (Davis et al. 2022). The prevalence of suicidal ideation in adults with AD, unless noted, is as follows: Suicidal ideation • 12.2% (multinational, meta-analysis; Patel et al. 2019) • 15.0% to 21.3% (EU; Dalgard et al. 2015; Dieris-Hirche et al. 2017) • 0.2% (South Korea, aged 13-18 years; Ahn et al. 2019) Suicide attempt • 6.6% (EU; Dieris-Hirche et al. 2017)
Allergic rhinitis	Allergic rhinitis is a recognised common co-morbidity of AD and a component of some diagnostic criteria for AD (Davis et al. 2022). The prevalence of allergic rhinitis in patients with AD is reported as follows: Adults • 51.3% patient-reported (multinational; Simpson et al. 2016) • 21.0% to 25.2% in Poland and Germany, respectively (Sybilski et al. 2015; Radtke et al. 2017) • 30% hay fever (US; Hanifin et al. 2007; Whiteley et al. 2016) • 27.3% to 30.5% (Taiwan; Wu et al. 2014; Cheng et al. 2015) • 36.9% patient-reported (Japan; Arima et al. 2018) Adolescents • 30.7% to 34.5% hay fever (US, aged <18 years; Shaw et al. 2011; Yaghmaie et al. 2013) • 42.9% (South Korea, aged 13-18 years; Ahn et al. 2019) • 7.1% (multinational, aged <18 years; Gilaberte et al. 2020)
Conjunctivitis	Prevalence of conjunctivitis varies greatly, as this is a clinically non-specific event that can have multiple aetiologies. The prevalence of conjunctivitis in patients with AD is reported as follows: Adults • 3.7% based on ICD-10 codes, and up to 18.9% based on treatment with anti-inflammatory topical ophthalmic products (Denmark; Thyssen et al. 2017)

Co-morbidity	Prevalence in AD Population (Unless Other Measure Noted)
	• 18.75% allergic conjunctivitis; 1.25% keratoconjunctivitis (Malaysia; Gan et al. 2022) • 12.7% current conjunctivitis at the time of survey, 66.6% lifetime prevalence (Denmark; Ronnstad et al. 2022) Adolescents • 14.3%, allergic conjunctivitis (South Korea, aged 13-18 years; Ahn et al. 2019) • 13.4% conjunctivitis (US, aged <18 years; Paller et al. 2022)
Asthma	Adults with AD are 3 times as likely to have asthma compared with general population (Davis et al. 2022). The prevalence of asthma in patients with AD is reported as follows: Adults • 24.8% in meta-analysis (Davis et al. 2022) • 40.3% patient-reported (multinational; Simpson et al. 2016) • 4.0% (Poland; Sybilski et al. 2015) to 17.77% (Germany; Radtke et al. 2017) • 22.4% to 33% (US; Hanifin et al. 2007; Whiteley et al. 2016) • 2.14% to 30.2% (Asia; Wu et al. 2014; Takaki and Ishii 2013) • 12.62% patient-reported (Japan; Arima et al. 2018) Adolescents • 22.8% to 25.2% (US, aged <18 years; Shaw et al. 2011; Yaghmaie et al. 2013) • 6.3% (South Korea, aged 13-18 years; Ahn et al. 2019) • 13.1% (multinational, aged <18 years; Gilaberte et al. 2020)
Food allergy	The odds of having food allergy among adults with AD compared with the general population increases with increasing AD severity. Among those with moderate AD, the RR was reported as 2.40 (95% CI: 1.54 to 3.27) and among those with severe AD, the RR was reported as 8.49 (95% CI: 5.44 to 11.54) (Davis et al. 2022). The prevalence of food allergy in patients with AD is reported as follows: Adults • 11% in meta-analysis (Davis et al. 2022) • 14.6% self-reported (US; Silverberg et al. 2018) Adolescents • 15.1% (US, aged 0-17 years; Yaghmaie et al. 2013)
Alopecia areata	Epidemiologic studies have shown an association between AD and AA (Mohan and Silverberg 2015). However, the magnitude of the association is unclear due to diagnostic bias. The prevalence of AA in patients with AD is reported as follows: Adults • 0.1% to 0.95% (US; Narla and Silverberg 2019; Andersen et al. 2017)

Co-morbidity	Prevalence in AD Population (Unless Other Measure Noted)
	Adolescents • 0.04% (US, aged 0-17 years; Narla and Silverberg 2019)
Skin infections	Patients with AD have dramatically increased odds of being colonised with *S. aureus* than controls on lesion skin (OR = 19.74, 95% CI: 10.88 to 35.81) (Totte et al. 2016). The prevalence of skin infections in patients with AD is reported as follows: • *S. aureus* colonisation 73% to 77.5% (Germany; Thum et al. 2013; Ong and Leung 2016; Clausen et al. 2017) • 70% for lesional skin, 39% non-lesional skin, 62% for the nose (multinational, meta-analysis; Totte et al. 2016) • 19% bacterial infections (impetiginised eczema, folliculitis, cellulitis) and 3% viral infections (eczema herpeticum, viral warts, molluscum contagiosum) (Singapore; Tay et al. 1999)
Herpes infections	Herpes simplex virus infections are more than twice as common among patients with AD compared with general population controls (Davis et al. 2022). The prevalence of herpes infections in patients with AD is reported as follows: • Eczema herpeticum 2% to 3% (Leung 2013; Blauvelt et al. 2017)
Cardiovascular disease	According to a recent guideline from the American Academy of Dermatology (Davis et al. 2022), there is mounting evidence for a small association between AD and various CV conditions. For stroke, myocardial infarction, and CV death, there may be a severity gradient with uncertain risk for adults with mild AD and potentially increased risk in adults with severe AD (Davis et al 2022). The incidence rate of various cardiac outcomes in patients with AD is reported as follows: Stroke • 0.27 per 100 PY (Denmark; Andersen et al. 2016) (UK; Silverwood et al. 2018) Myocardial infarction • 0.20 per 100 PY (Denmark; Andersen et al. 2016) (UK; Silverwood et al. 2018) CV Death • 0.29 to 0.44 per 100 PY (Denmark; Andersen et al. 2016) (UK; Silverwood et al. 2018)
Skin cancer	Data for skin cancers, including melanoma and non-melanoma skin cancers, are mixed, with some literature suggesting increased risks for adults with AD, and others suggesting no risk (Andersen et al. 2017; Paller et al. 2018). The incidence rate of skin cancer in patients with AD is reported as follows: Melanoma • 0.04 per 100 PY (US; Hedderson et al. 2021) • 0.02 per 100 PY (UK; Arana et al. 2010) • 0.03 per 100 PY (England; Mansfield et al. 2020) Non-melanoma Skin Cancer • 0.48 per 100 PY (US; Hedderson et al. 2021) • 0.88 per 100 PY (UK; Arana et al. 2021)

Co-morbidity	Prevalence in AD Population (Unless Other Measure Noted)
	• 0.29 per 100 PY (England; Mansfield et al. 2020)
CTCL/mycosis fungoides	Prevalence of CTCL and mycosis fungoides is not directly available within an AD population. There is a slightly increased risk of lymphoma in adults with AD, with severity of AD as a significant risk factor (Legendre et al. 2015; Paller et al. 2018; Mansfield et al. 2020). For example, the risk of NHL in patients with AD increased with increasing severity versus those without AD (HR = 1.06 for mild AD, HR = 1.24 for moderate AD, HR = 2.08 for severe AD) (Mansfield et al. 2020). • CTCL is a relatively rare subtype of NHL, comprising 2% to 3% of all NHL cases (Phan et al. 2016)

Abbreviations: AA = alopecia areata; AD = atopic dermatitis; CI = confidence interval; CTCL = cutaneous T-cell lymphoma; CV = cardiovascular; ICD-10 = International Statistical Classification of Diseases and Related Health Problems 10th Revision; NHL = non-hodgkin lymphoma; OR = odds ratio; PY = patient-years; RR = relative risk.

Module SII – Non-clinical Part of the Safety Specification

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

SII.1 Toxicity

Repeat-Dose toxicity

Non-clinical toxicity findings attributed to lebrikizumab and of potential clinical significance were limited to subcutaneous ISRs. Swelling in the area of injection was identified in 1 monkey and did not worsen with repeated dosing.

ISRs were reported with a low frequency (3.1%) in lebrikizumab-treated patients across all AD studies. All events were non-serious and most patients (94.3%) reported events with mild or moderate severity.

Carcinogenicity

Carcinogenicity studies of lebrikizumab have not been conducted. No tumours or precancerous lesions were observed in monkeys that received lebrikizumab for up to 9 months. Among lebrikizumab-treated patients across all AD studies, a total of 13 (0.8%) patients reported 20 events of malignancy, of which 10 events from 5 patients were NMSC. All the NMSC events were non-serious. Malignancies other than non-NMSC reported among lebrikizumab-treated patients across all AD studies were mostly single events with no trend in the type of tumours.

Reproductive or developmental toxicity

No significant effects were observed related to reproductive or developmental toxicity in sexually mature or pregnant monkeys who received lebrikizumab.

SII.2 Safety Pharmacology

No significant cardiovascular, respiratory, or central nervous system findings were observed in monkeys who received lebrikizumab.

SII.3 Other Toxicity-Related Information or Data

Not applicable, as there were no other clinically relevant findings in non-clinical studies.

Module SIII - Clinical Trial Exposure

Clinical trial exposure of lebrikizumab is presented from 8 clinical studies that were designed to evaluate the efficacy and safety of lebrikizumab in patients with AD:

- one Phase 2, randomised open-label Study ARBAN (J2T-DM-KGAH [KGAH])
- 5 multicentre, randomised, double-blind, placebo-controlled studies, which include
    - two Phase 2 Studies TREBLE (J2T-DM-KGAG [KGAG]) and J2T-DM-KGAF (KGAF), and
    - three Phase 3 Studies ADvocate 1 (J2T-DM-KGAB [KGAB]), ADvocate 2 (J2T-DM-KGAC [KGAC]), and ADhere (J2T-DM-KGAD [KGAD])
- one Phase 3 long-term safety Study ADjoin (J2T-DM-KGAA [KGAA]), and
- one Phase 3, open-label, adolescent single arm Study ADore (J2T-DM-KGAE [KGAE]).

Additional clinical studies evaluating lebrikizumab in patients with asthma, COPD, IPF, and RHL have also been conducted. A total of 3317 patients with asthma were exposed to any dose of lebrikizumab in Phase 1 to 3 studies. During early phase studies of lebrikizumab in COPD, RHL, and IPF studies, a total of 429 patients were exposed to any dose of lebrikizumab.

Table SIII.1. Duration of Lebrikizumab Exposure

Atopic Dermatitis ***Atopic Dermatitis All Lebrikizumab Exposure Modified Safety Population[a]***		
Duration of Exposure (Weeks)	**Patients**	**Patient-Years**
>0 to <4	23	0.9
≥4 to <16	130	24.7
≥16 to <24	266	99.2
≥24 to <32	120	65.6
≥32 to <40	183	117.2
≥40 to <52	116	102.3
≥52 to <78	613	749.9
≥78 to <104	210	344.1
≥104	59	133.1
Total	1720	1637.0

Abbreviations: AD = atopic dermatitis; GCP = good clinical practice.

[a] This population is comprised of patients who received at least 1 dose of study drug in lebrikizumab AD clinical Studies KGAG, KGAH, KGAF, KGAB, KGAC, KGAD, KGAE, and KGAA (as of the data cutoff 06 June 2022). A total of 36 patients exposed to lebrikizumab from 1 study site participating in Studies KGAA, KGAC, and KGAD are excluded from this analysis set due to GCP non-compliance related to protocol entry criteria.

Time spent within any temporary study drug interruption is included within exposure time. Time after permanent study drug discontinuation is not included within exposure time. Total patient-years is calculated as sum of duration of exposure in days for all patients in dosing regimen divided by 365.25.

Table SIII.2. Age Group and Gender

Age Group *Atopic Dermatitis All Lebrikizumab Exposure Modified Safety Population*[a]	**Patients**		**Patient-Years**	
	M	**F**	**M**	**F**
<65 years				
≥12 to <18 years	172	200	193.8	219.3
≥18 to <30 years	240	264	204.3	234.5
≥30 to <50 years	236	220	216.5	194.9
≥50 to <65 years	124	141	113.0	145.1
≥65 years				
≥65 to <75 years	55	39	57.8	35.1
≥75 to <85 years	15	9	12.4	6.8
≥85 years	1	4	0.5	2.9
Total	843	877	798.4	838.7

Abbreviations: AD = atopic dermatitis; F = female; GCP = good clinical practice; M = male.

[a] This population is comprised of patients who received at least 1 dose of study drug in lebrikizumab AD clinical Studies KGAG, KGAH, KGAF, KGAB, KGAC, KGAD, KGAE, and KGAA (as of the data cutoff 06 June 2022). A total of 36 patients exposed to lebrikizumab from 1 study site participating in Studies KGAA, KGAC, and KGAD are excluded from this analysis set due to GCP non-compliance related to protocol entry criteria.

Time spent within any temporary study drug interruption is included within exposure time. Time after permanent study drug discontinuation is not included within exposure time. Total patient-years is calculated as sum of duration of exposure in days for all patients in dosing regimen divided by 365.25.

Table SIII.3. Dose

Dose of Exposure ***Atopic Dermatitis All Lebrikizumab Exposure Modified Safety Population***[a]	**Patients**	**Patient-Years**
LEB 250 Q4W[b]	245	229.1
LEB 250 Q2W[c]	1367	1301.7
LEB 125 Q4W	152	66.0
Other doses (250 mg single dose + TCS, 125 mg single dose + TCS)	105	40.2
Total (any LEB)	1720	1637.0

Abbreviations: AD = atopic dermatitis; GCP = good clinical practice; LEB = Lebrikizumab; Q2W = every 2 weeks; Q4W = every 4 weeks; TCS = topical corticosteroids.

[a] This population is comprised of patients who received at least 1 dose of study drug in lebrikizumab AD clinical Studies KGAG, KGAH, KGAF, KGAB, KGAC, KGAD, KGAE, and KGAA (as of the data cutoff 06 June 2022). A total of 36 patients exposed to lebrikizumab from 1 study site participating in Studies KGAA, KGAC, and KGAD are excluded from this analysis set due to GCP non-compliance related to protocol entry criteria.

[b] Includes all patients who were ever exposed to LEB 250 mg Q4W during the trial.

[c] Includes all patients who were ever exposed to LEB 250 mg Q2W during the trial.

Time spent within any temporary study drug interruption is included within exposure time. Time after permanent study drug discontinuation is not included within exposure time. Total patient-years is calculated as sum of duration of exposure in days for all patients in dosing regimen divided by 365.25.

Table SIII.4. Ethnic Origin

Ethnic Origin ***Atopic Dermatitis All Lebrikizumab Exposure Modified Safety Population***[a]	**Patients**	**Patient-years**
American Indian or Alaska Native	26	25.3
Asian	311	301.6
Black or African American	232	203.0
Native Hawaiian or other Pacific Islander	9	9.1
White	1079	1039.0
Multiple	40	40.8
Other	17	14.8
Not reported	5	3.1
Unknown	1	0.4
Total	1720	1637.0

Abbreviations: AD = atopic dermatitis; GCP = good clinical practice

[a] This population is comprised of patients who received at least 1 dose of study drug in lebrikizumab AD clinical Studies KGAG, KGAH, KGAF, KGAB, KGAC, KGAD, KGAE, and KGAA (as of the data cutoff 06 June 2022). A total of 36 patients exposed to lebrikizumab from 1 study site participating in Studies KGAA, KGAC, and KGAD are excluded from this analysis set due to GCP non-compliance related to protocol entry criteria.

Time spent within any temporary study drug interruption is included within exposure time. Time after permanent study drug discontinuation is not included within exposure time. Total patient-years is calculated as sum of duration of exposure in days for all patients in dosing regimen divided by 365.25.

Module SIV - Populations Not Studied in Clinical Trials

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

Criterion: Patients younger than 12 years and adolescent patients (12 years and older) weighing less than 40 kg

Reason for exclusion: The safety and efficacy of lebrikizumab have not been established for

- patients younger than 12 years, and
- adolescent patients (12 years and older) weighing less than 40 kg.

To establish the efficacy and safety of lebrikizumab, Phase 3 clinical trials were conducted first in adults and adolescents (12 years and older who weigh at least 40 kg). Additional Phase 3 studies in the paediatric and adolescent populations are currently planned.

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

Rationale: The prescribing information will clearly state that the safety and efficacy of lebrikizumab in children below the age of 12 years and adolescents aged 12 to 17 years weighing less than 40 kg have not yet been established. Additionally, approved, alternative therapeutic options are available for the treatment of AD in these paediatric or adolescent patients. It was agreed with regulatory agencies of the US and the EU to start studies in other paediatric populations once a positive risk-benefit in adults and adolescents aged at least 12 years has been established. Additional Phase 3 studies in the paediatric and adolescent populations are currently planned.

Criterion: Pregnant or breastfeeding women

Reason for exclusion: This is a standard exclusion criterion in clinical development. Although no significant effects were observed related to reproductive or developmental toxicity in sexually mature or pregnant monkeys who received lebrikizumab, there are insufficient human data to establish the safety of lebrikizumab during pregnancy and lactation.

Is it considered to be included as missing information?: Yes

Rationale: Not applicable.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

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

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

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

Type of special population	Exposure
Pregnant women	Pregnancy was an exclusion criterion in the clinical development programme.
Breastfeeding women	Not included in the clinical development programme.
Patients with relevant co-morbidities: Patients with hepatic impairment Patients with cardiovascular impairment Immunocompromised patients	Lebrikizumab has not been specifically studied in patients with these co-morbidities.
Patients with uncontrolled severe asthma Patients with prior history of anaphylaxis	Severe and uncontrolled asthma and prior history of anaphylaxis were exclusion criteria in the AD clinical development programme.
Patients using live vaccine	Patients who received live vaccines were excluded from trials in the AD clinical development programme.
Patients with a disease severity different from inclusion criteria in clinical trials	The clinical development programme included patients with moderate to severe AD. Patients with mild disease were not specifically studied.
Patients with renal impairment	Lebrikizumab has not been specifically studied in patients with renal impairment. In the AD clinical development programme, 33 (2.4%) patients with moderate decrease in eGFR (≥30 and <60 mL/min/1.7m2) and 2 (0.1%) patients with severe decrease in eGFR (≥15 and <30 mL/min/1.7m2) were exposed to lebrikizumab. No patients with end stage renal disease (eGFR <15 mL/min/1.7m2) were included in AD clinical development programme.
Population with relevant different ethnic origin	Per data presented in Table SIII.4, the distribution of patients of different ethnic origins is generally reflective of the anticipated target population.
Subpopulations carrying relevant genetic polymorphisms	Not applicable. Patient-level genetic polymorphisms were not specifically studied in the clinical development programme.

Abbreviations: AD = atopic dermatitis; eGFR = estimated glomerular filtration rate.

Module SV - Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

Lebrikizumab 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 of lebrikizumab for illegal purposes is not considered to be a significant risk, particularly in the absence of associated euphoric or other central nervous system effects associated with addictive behaviour. This class is not known to produce dependence syndromes. In clinical studies of lebrikizumab to date, there have been no findings indicating that lebrikizumab causes physical or mental dependency.

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:

- Conjunctivitis: For the AD Induction Period Placebo-Controlled Integrated Analysis Set (AD ALL PC Weeks 0 to 16), conjunctivitis was reported for 67 (8.6%) patients receiving lebrikizumab 250 mg Q2W compared with 10 (2.5%) patients receiving placebo. All events of conjunctivitis were non-serious and mild or moderate in severity. A total of 3 (0.4%) patients receiving lebrikizumab 250 mg Q2W discontinued the study treatment due to conjunctivitis.

  For AD All Lebrikizumab Exposure Analysis Set (AD ALL LEB), conjunctivitis events were reported in 10.6% patients treated with lebrikizumab. Events were non-serious and mostly mild-to-moderate in intensity (97.4%). A total of 17 (1.0%) patients discontinued the study treatment due to conjunctivitis.

- Keratitis: For AD ALL PC Weeks 0-16, keratitis was reported for 5 (0.6%) patients receiving lebrikizumab 250 mg Q2W compared to 1 (0.2%) patient receiving placebo during the Induction Period. All events of keratitis were non-serious and moderate in severity. A total of 2 (0.3%) patients receiving lebrikizumab 250 mg Q2W discontinued the study treatment due to keratitis.

  For AD ALL LEB, keratitis events were reported in 9 (0.5%) patients treated with lebrikizumab. A total of 3 (0.2%) patients discontinued the study treatment due to keratitis. Events were non-serious and mainly mild or moderate in severity (92.8%).

- ISRs: For AD ALL PC Weeks 0-16, ISRs were reported for 20 (2.6%) patients receiving lebrikizumab 250 mg Q2W compared with 6 (1.5%) patients receiving placebo. All ISR events were non-serious. Except for 1 patient receiving lebrikizumab, all the ISR events were mild or moderate in severity. A total of 2 (0.3%) patients discontinued the study treatment due to ISR.

  For AD ALL LEB, ISR events were reported in 3.1% patients treated with lebrikizumab. All events were non-serious, and most patients (94.3%) reported

events with mild or moderate severity. A total of 5 (0.3%) patients discontinued the study treatment due to ISR.

- Eosinophilia: For AD ALL PC Weeks 0 to 16, blood eosinophil increased to severe category (more than 5000 cells per microlitre) for 3 (0.4%) patients receiving lebrikizumab 250 mg Q2W compared to 0 patients receiving placebo.

  For AD ALL LEB, blood eosinophil increased to severe category (more than 5000 per microlitre) for 8 (0.5%) patients.

  In general, the eosinophilia was transient, did not result in discontinuation and was not associated with adverse events.

- Herpes zoster: For AD ALL PC Weeks 0 to 16, herpes zoster was reported for 5 (0.6%) patients receiving lebrikizumab 250 mg Q2W compared with 0 patients receiving placebo. All events of herpes zoster were non-serious, mild or moderate in severity and none led to discontinuation.

  For AD ALL LEB, herpes zoster events were reported in 14 (0.8%) patients treated with lebrikizumab. No patients discontinued the study treatment due to herpes zoster. All events were non-serious and mild or moderate in severity.

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 Risk: None

Important Potential Risk: None

Missing Information 1: Use in pregnant and breastfeeding women

Risk-benefit impact:

The current data are too limited to draw conclusions about the effect of lebrikizumab exposure during pregnancy and lactation in humans.

No significant effects were observed related to reproductive or developmental toxicity in sexually mature or pregnant monkeys who received lebrikizumab. There were no effects on reproductive organs or fertility parameters assessed in sexually mature females (menstrual cycling, reproductive hormones) or males (semen or sperm analysis). Administration of lebrikizumab to pregnant monkeys throughout organogenesis in an embryo-foetal development study and throughout organogenesis through parturition in a pre- and postnatal development study identified no embryo-

foetal toxicity or adverse effects on the growth, development, or immune system function of offspring.

Pregnant women were excluded from entering lebrikizumab clinical studies. Women of child-bearing potential were included after agreeing to comply with protocol-specified pregnancy testing and contraceptive requirements, and male participants were not required to use contraception. Pregnancies that occurred in female clinical trial participants was a criterion for permanent discontinuation of lebrikizumab in all studies, and pregnant participants and partner pregnancies who consented are followed up until pregnancy completion.

Cumulatively, there have been 1421 females of reproductive potential enrolled in lebrikizumab clinical trials for AD and asthma. These patients are defined by the Centers for Disease Control and Prevention as females aged between 15 to 44 years.

Across all indications, there are limited safety data on the use of lebrikizumab in pregnant women. As of 06 June 2022, there have been 20 pregnancies from maternal exposure and 5 from paternal exposure reported during the lebrikizumab clinical development programme. There has been no case of exposure to lebrikizumab during lactation.

Although the risk of lebrikizumab to pregnant women with AD is not expected to be different, lebrikizumab will be used among women of childbearing age and there is currently insufficient information to draw conclusions about the safety of exposure during pregnancy. As such, use during pregnancy is considered missing information. An observational database study will be conducted post-approval as a part of the pharmacovigilance plan because of the limited data on pregnancy outcomes. The objectives of the study are 2-fold:

- to estimate occurrence of pregnancy and infant outcomes among women exposed to lebrikizumab in pregnancy.
- if the sample size permits, to evaluate the relative risk of the adverse pregnancy and infant outcomes among women with AD exposed to lebrikizumab in pregnancy compared to women with AD unexposed to lebrikizumab in pregnancy.

Should emerging experience of such use in pregnancy reveal clinically significant adverse outcomes to the mother, foetus, baby, or all, this could have an impact on the risk-benefit of lebrikizumab use in female patients with AD.

Missing Information 2: Long-term safety of lebrikizumab.

Risk-benefit impact:

Moderate--to--severe AD is a complex and chronic disease requiring treatment for long periods of time. The maximum treatment exposure duration is 939 days in the AD clinical development programme. Additional clinical studies to evaluate lebrikizumab in patients with asthma, COPD, IPF, and RHL have also been conducted. There has been no patient exposure outside of the clinical development programme. As such, long-term safety of lebrikizumab is considered missing information. The ongoing Study KGAA evaluates the long-term safety and efficacy of lebrikizumab in patients with moderate-to-severe AD and is a part of the pharmacovigilance plan

for further characterising long-term safety. Additionally, patients enrolled at centres in Germany and Poland who complete Study KGAA are eligible to participate in the ongoing, long-term safety and efficacy study M-17923-32, which will provide up to 2 additional years of treatment. Cumulative data from the parent study plus studies KGAA and M-17293-32 will enable collection of lebrikizumab safety data for up to a total of 5 years of continuous treatment.

If the data demonstrate that long-term lebrikizumab use is associated with adverse outcomes or morbidity, this could have an impact on the risk-benefit of lebrikizumab use in the context of a chronic and relapsing disease, which when left untreated or uncontrolled can have a significant impact on sleep, mood, anxiety, and social function.

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

Not applicable, as a European Union Risk Management Plan has not previously been submitted.

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 Risk: None

Important Potential Risk: None

SVII.3.2 Presentation of the Missing Information

Missing Information: Use in pregnant and breastfeeding women.

Evidence source:

Cumulatively as of 06 June 2022, there were 25 pregnancies across all lebrikizumab indications. Of these, 10 were reported in the AD clinical development programme and 15 occurred during the asthma interventional studies.

A total of 20 women became pregnant during their lebrikizumab study participation, and partners of 5 male participants became pregnant during the male participant's lebrikizumab study participation.

As shown in Table SVII., within the 25 pregnancies, 19 cases reported pregnancy outcomes, and 6 cases were still in utero or lost to follow-up.

Table SVII.1. Neonate Birth Type in Lebrikizumab Clinical Trials by Indication

Neonate Birth Type	Atopic Dermatitis Clinical Trials[a]	Asthma Clinical Trials[b]	All Lebrikizumab Clinical Trials
Elective termination	4	2	6
Full-term	3	4	7
Spontaneous abortion	0	6	6
In utero[c]	3	3	6
Total	10	15	25

[a] Includes pregnancies reported in lebrikizumab atopic dermatitis clinical Studies KGAA, KGAB, KGAC, KGAF, and KGAL (as of the data cutoff 06 June 2022).

[b] Includes pregnancies reported in lebrikizumab asthma clinical Studies KGAN, KGAO, KGAP, KGAS, and KGAT (as of the data cutoff 06 June 2022).

[c] Some cases reported as in utero have been lost to follow-up.

Definitions: Elective termination = a pregnancy that was electively terminated; Full-term = an infant born between 37 and 42 weeks of gestation; In utero = in the uterus, unborn; Spontaneous abortion = failure of embryonic development and expulsion of all or any part of the product of conception before 20 weeks gestation or expulsion of a foetus weighing less than 500 grams.

Seven (28.0%) pregnancies were reported with neonatal outcomes, all of which were full-term (Table SVII.). For the 7 pregnancies followed up to delivery across the lebrikizumab clinical development programme, no neonatal congenital anomalies were reported. Perinatal complications were reported in 2 neonates, 1 developed neonatal jaundice, and 1 had foetal growth restriction and hypoglycaemia.

Trimester of exposure was reported for 19 (76.0%) pregnancies. In 17 of these pregnancies, exposure occurred in the first trimester of gestation. The 2 cases who reported exposure during all trimesters had full-term birth with normal neonate outcome.

Although the mechanism of action, non-clinical data, and clinical trial data do not indicate that the safety profile of lebrikizumab is expected to be different in pregnant and lactating women, there are insufficient data to establish the safety of lebrikizumab during pregnancy and lactation in humans.

Population in need of further characterisation:

Pregnant women with moderate--to--severe AD.

Anticipated risk/consequence of the missing information:

The safety profile of lebrikizumab use in pregnant women with moderate--to--severe AD is unknown.

Missing Information: Long-term safety of lebrikizumab

Evidence source:

The long-term safety of lebrikizumab beyond 52 weeks of treatment duration has not been established through the AD clinical programme. As AD is a chronic and relapsing condition, the

long-term use of lebrikizumab may occur in clinical practice. There remains a need to obtain long-term safety data.

Population in need of further characterisation:

Patients with moderate--to--severe AD receiving long-term treatment with lebrikizumab beyond the 52 weeks of treatment.

Anticipated risk/consequence of the missing information:

It could be anticipated that with long-term use, adverse events that are infrequent or have a longer latency period could occur.

Module SVIII - Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in pregnant and breastfeeding women Long-term safety of lebrikizumab

Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

None proposed.

III.2 Additional Pharmacovigilance Activities

Study Short Name and Title: Observational Database Study of Pregnancy and Infant Outcomes among Women Exposed to Lebrikizumab During Pregnancy

Rationale and Study Objectives:

Pregnant women were excluded from lebrikizumab clinical trials, and if a pregnancy did occur during the trial, the patient permanently discontinued study drug. Developmental toxicity studies in pregnant cynomolgus monkeys revealed no evidence of harm to the foetus or infant.

However, the indicated population for lebrikizumab includes women of childbearing age. Given the limited information available on pregnancy outcomes, an observational study is warranted in the post-marketing setting.

This study aims to evaluate the safety of lebrikizumab in pregnant women and their infants. The safety outcomes of interest include pregnancy outcomes (recognized spontaneous abortion, stillbirth, preterm birth) and infant outcomes (small for gestational age, major congenital malformations). There are 2 study objectives:

1. To estimate occurrence of pregnancy and infant outcomes among women exposed to lebrikizumab in pregnancy.
2. If the sample size permits, to evaluate the relative risk of the adverse pregnancy and infant outcomes among women with AD exposed to lebrikizumab in pregnancy compared to women with AD unexposed to lebrikizumab in pregnancy.

Study Design:

Observational cohort study using secondary data from a US-based administrative claims database where de-identified records of mothers and their offspring can be linked with high accuracy.

Study Population:

The descriptive objective (objective #1) will include all women exposed to lebrikizumab in pregnancy ("lebrikizumab cohort"). To minimize confounding by indication and inform relative safety of lebrikizumab in pregnancy, the comparative objective (objective #2) will be addressed among women with AD. The study cohorts for the comparative objective will include women exposed to lebrikizumab with a diagnosis of AD ("lebrikizumab AD cohort"); and a reference cohort of women with a diagnosis of AD who are not exposed to an IL-13 inhibitor in pregnancy ("non-IL-13 inhibitor AD cohort").

Milestones:

Milestone	Planned Date
Submission of protocol	Within 6 months of European Commission decision anticipated 31 May 2024
Start of data collection/extraction	Within 2 years of first regulatory approval
Study Progress Reports	Included in PSUR[§]
End of data collection/extraction	31 September 2030
Final report of study results	Estimated 31 September 2031

[§] After start of data collection/extraction

Study Short Name and Title: A long-term study to assess the safety and efficacy of lebrikizumab in patients with moderate-to-severe atopic dermatitis (J2T-DM-KGAA).

Rationale and Study Objectives:

The objective of Study KGAA is to evaluate the long-term safety and efficacy of lebrikizumab in patients with moderate-to-severe AD.

The primary endpoint of the study is to describe proportion of patients discontinued from study treatment due to adverse events through the last treatment visit.

Additionally, long-term safety will be assessed over the 100-week study by monitoring the collection of adverse events, serum chemistry and haematology laboratory testing, physical examination, and vital signs.

Study Design:

Study KGAA is a 100-week, non-randomised, Phase 3 interventional study to assess the long-term safety and efficacy of lebrikizumab for moderate-to-severe AD. Patients who have completed participation in 1 of the qualifying parent Studies KGAB, KGAC, KGAD, KGAE, or J2T-MC-KGAK (KGAK), are offered the opportunity to enrol in this study.

Two treatment regimens are assessed:

- 250-mg lebrikizumab, administered Q2W and
- 250-mg lebrikizumab, administered every 4 weeks.

The regimen assigned to each patient is based on the treatment received in the patient's respective parent trial.

There is an addendum Study KGAA (1) for approximately 100 patients to enrol directly into an open-label treatment arm for Study KGAA. These patients receive open-label lebrikizumab 250 mg Q2W after 2 loading doses of 500 mg at Baseline and at Week 2.

Study Population:

Adolescent (12 to less than 18 years weighing at least 40 kg) and adult patients with moderate-to-severe AD who completed a prior lebrikizumab Study KGAB, KGAC, KGAD, KGAE, or KGAK, are expected to enroll in this study.

Study Short Name and Title: Long-term safety and efficacy of lebrikizumab in adult and adolescent patients with moderate-to-severe atopic dermatitis (M-17923-32).

Rationale and Study Objectives:

The objective of Study 17923-32 is to examine the long-term safety and efficacy of lebrikizumab in adults and adolescents with moderate-to-severe AD. Patients enrolled in Study KGAA at centres in Germany and Poland who complete the study are eligible to participate in M-17923-32. Cumulative data from the parent study plus studies KGAA and M-17293-32 will enable collection of lebrikizumab safety data for a total of up to 5 years of continuous treatment.

The primary endpoint of the study is the proportion of patients discontinued from study treatment due to treatment-emergent AEs through the last study visit.

Safety will also be assessed based on the incidence of AEs, including serious AEs and AEs of special interest.

Study Design:

Study M-17923-32 is an open-label study to assess the long-term safety and efficacy of in adult and adolescent patients with moderate-to-severe AD.

All patients receive open-label treatment with lebrikizumab 250 mg administered every 4 weeks (Q4W), regardless of their treatment regimen in Study KGAA. If patient's response is less than a 50% reduction from baseline in the Eczema Area and Severity Index (EASI50), lebrikizumab dosing frequency may be increased to Q2W at any time during the course of the study; thereafter, lebrikizumab Q4W dosing may be resumed at the Investigator's discretion.

Study Population:

Adult and adolescent (12 to <18 years and weighing ≥ 40 kg) patients with moderate-to-severe AD. The study is open to patients enrolled in Study KGAA at centres in Germany and Poland who completed the study.

III.3 Summary Table of Additional Pharmacovigilance Activities

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

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Estimated Due Dates
Category 3 - Required additional pharmacovigilance activities				
Post-marketing observational study of pregnancy and infant outcomes among women exposed to lebrikizumab during pregnancy in US-based Administrative Claims Data *Planned*	Objectives include: • to estimate occurrence of pregnancy and infant outcomes among women exposed to lebrikizumab in pregnancy. • If the sample size permits, to evaluate the relative risk of the adverse pregnancy and infant outcomes among women with AD exposed to lebrikizumab in pregnancy compared to women with AD unexposed to lebrikizumab in pregnancy.	*Missing information:* Use in pregnant women	*Protocol* *Final Study Report*	*Within 6 months of EC decision, anticipated 31 May 2024* *31 September 2031*
A long-term study to assess the safety and efficacy of lebrikizumab in patients with moderate-to-severe atopic dermatitis (J2T-DM-KGAA) *Ongoing*	To evaluate the long-term safety and efficacy of lebrikizumab in patients with moderate-to-severe AD.	*Missing information:* Long-term safety of lebrikizumab	*Final Study Report*	*February 2025*

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Estimated Due Dates
Category 3 - Required additional pharmacovigilance activities				
Long-term safety and efficacy of lebrikizumab in adult and adolescent patients with moderate-to-severe atopic dermatitis (M-17923-32)	To evaluate the long-term safety and efficacy of lebrikizumab in patients with moderate-to-severe AD.	*Missing information:* Long-term safety of lebrikizumab	*Protocol* *Final study report*	*05 April 2023 (first version approved by the Competent Authority)* *August 2026*

Abbreviation: AD = atopic dermatitis; AE=adverse event; FPFV=first patient, first visit; LPLV=last patient, last visit; Q4W=every 4 weeks.

Part IV: Plans for Post-Authorisation Efficacy Studies

Not applicable

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

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

Safety Concern	Routine Risk Minimisation Activities
Use in pregnant and breastfeeding women	Routine risk communication: • SmPC Section 4.6 • PL Section 2, Pregnancy, breast-feeding and fertility Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.6 recommends avoiding the use of lebrikizumab in pregnancy. The use during lactation should be evaluated taking into account the potential benefit-risk. • PL Section 2, Pregnancy, breast-feeding and fertility recommends that it is preferable to avoid the use of Ebglyss in pregnancy and lactation unless your doctor advises to use it. Pack size: Not applicable Legal status: Not applicable
Long-term safety of lebrikizumab	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Pack size: Not applicable Legal status: Available by prescription only

Abbreviations: SmPC = Summary of product characteristics, PL = Package leaflet

V.2 Additional Risk Minimisation Measures

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

V.3 Summary of Risk Minimisation Measures

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

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in pregnant and breastfeeding women	Routine risk minimisation measures: SmPC Section 4.6 PL Section 2 Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None proposed. Additional pharmacovigilance activities (Pregnant woman): • Observational database study of pregnancy and infant outcomes among women exposed to lebrikizumab during pregnancy
Long-term safety of lebrikizumab	Routine risk minimisation: None Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None proposed Additional pharmacovigilance activities: • A long-term study to assess the safety and efficacy of lebrikizumab in patients with moderate-to-severe atopic dermatitis (J2T-DM-KGAA) • Long-term safety and efficacy of lebrikizumab in adult and adolescent patients with moderate-to-severe atopic dermatitis (M-17923-32)

Abbreviations: SmPC = Summary of product characteristics, PL = Package leaflet

Part VI: Summary of the risk management plan for Ebglyss (Lebrikizumab)

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

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

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

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

I. The medicine and what it is used for

Ebglyss is authorised for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years of age and older with a body weight of at least 40 kg who are candidates for systemic therapy (see SmPC for the full indication). It contains lebrikizumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Ebglyss's benefits can be found in Ebglyss's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

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

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

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

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

Together, these measures constitute routine risk minimisation measures.

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

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

II.A List of important risks and missing information

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

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	Use in pregnant and breastfeeding women Long-term safety of lebrikizumab

II.B Summary of important risks

Missing information: Use in pregnant and breastfeeding women	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 recommends avoiding the use of lebrikizumab in pregnancy. The use during lactation should be evaluated taking into account the potential benefit-risk.

	PL Section 2, Pregnancy, breast-feeding and fertility recommends that it is preferable to avoid the use of Ebglyss in pregnancy and lactation unless your doctor advises to use it. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities (Pregnant Women): Observational database study of pregnancy and infant outcomes among women exposed to lebrikizumab during pregnancy See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Long-term safety of lebrikizumab	
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A long-term study to assess the safety and efficacy of lebrikizumab in patients with moderate-to-severe atopic dermatitis (J2T-DM-KGAA) • Long-term safety and efficacy of lebrikizumab in adult and adolescent patients with moderate-to-severe atopic dermatitis (M-17923-32) See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

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

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

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

Study Short Name: Observational Database Study of Pregnancy and Infant Outcomes Among Women Exposed to Lebrikizumab During Pregnancy

Purpose of the study:

To estimate the occurrence of certain adverse pregnancy and infant outcomes among women exposed to lebrikizumab in pregnancy. If the sample size permits, the study aims to estimate the relative risk of the adverse pregnancy and infant outcomes among women with AD exposed to lebrikizumab in pregnancy compared to women with AD unexposed to lebrikizumab in pregnancy.

Study Short Name: A long-term study to assess the safety and efficacy of lebrikizumab in patients with moderate-to-severe atopic dermatitis (J2T-DM-KGAA)

Purpose of the study:

To evaluate the long-term safety and efficacy of lebrikizumab in patients with moderate-to-severe atopic dermatitis up to 100 weeks.

Study Short Name: Long-term safety and efficacy of lebrikizumab in adult and adolescent patients with moderate-to-severe atopic dermatitis (M-17923-32)

Purpose of the study:

To evaluate the long-term safety and efficacy of lebrikizumab in patients with moderate-to-severe atopic dermatitis for up to 2 additional years.

Part VII: Annexes

Annex **Page**

Annex 4. Specific adverse drug reaction follow-up forms

None

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

Not applicable