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# EU Risk Management Plan
# Tralokinumab

Version: 3.0

LEO Pharma A/S

Date of report: 25-Jun-2025

# EU Risk Management Plan (RMP) for tralokinumab

**RMP version to be assessed as part of this application:**

RMP Version number: 3.0

Data lock point for this RMP: 31 Oct 2024

Date of final sign-off: Presented as an electronical signature on the last page of this document.

Rationale for submitting an updated RMP:

From RMP version 2.1 to 3.0

As agreed with EMA, a final major version (version 3.0) of the submitted updated RMP document (version 2.1) should be included in the response package of the ECZTEND submission. The changes to the updated RMP version 2.1 were accepted by EMA, and the only changes from version 2.1 to 3.0 of the RMP are the version number and date of report.

From RMP version 2.0 to 2.1

The ECZTEND trial is a phase 3 open-label, single-arm, multi-centre, long-term extension post-authorisation safety study (PASS) to evaluate the safety and efficacy of tralokinumab in subjects with atopic dermatitis who participated in previous tralokinumab clinical trials. ECZTEND is listed as an additional pharmacovigilance activity for Adtralza®. Therefore, the RMP was updated to reflect the finalization of the ECZTEND study. The report has now been finalized and is being submitted with this RMP update.

Based on the study results and accumulated knowledge of the product, the safety profile of Adtralza® has been re-evaluated. Consequently, LEO Pharma A/S (hereafter referred to as LEO Pharma) is proposing to remove the Important potential risks “Malignancy” and “Conjunctivitis” and the safety concern of missing information “Long-term safety” in the RMP. The justification for removing the three safety concerns is that, in accordance with the *GVP Module V – Risk Management Systems*, there are no additional pharmacovigilance activities or additional risk minimisation measures linked to the three safety concerns after the finalization of ECZTEND, and that the safety concerns are considered adequately monitored by routine pharmacovigilance activities.

Justification for removal of each safety concern can be found in Section SVII.2 New safety concerns and reclassification with a submission of an updated RMP. Further data is provided

in the Clinical Overview Addendum and study reports, which are presented as part of the ECZTEND submission.

The total post-marketing exposure has been updated with data from an additional 2.5 years' experience since the last RMP and the calculation method has been updated to capture both the prefilled pen and prefilled syringe. In addition, the clinical trial patient exposure was updated as clinical trials have been completed, and the post-authorization experience was updated with current data.

Summary of significant changes in this RMP is included in Table 1 below.

**Table 1 Summary of significant changes in this RMP**

| Part | Module | Significant changes made |
|---|---|---|
| II | SIII | Data Lock Point updated to 31 Oct 2024 |
| II | SIII | Exposure in clinical trials updated |
| II | SIV. 3 | Table 15 – Exposure of special populations included or not included in clinical trial development programmes updated |
| II | SV | Post-authorisation experience updated: Exposure calculation for prefilled pen added |
| II | SVII.1.2. | Table 17 – Summary of safety concerns: The three safety concerns Malignancy, Conjunctivitis, and Long-term safety have been removed from the table. |
| II | SVII.2 | Section: New safety concerns and reclassification with a submission of an updated RMP.<br>Justification for removal of the safety concern: Malignancy |
| II | SVII.2 | Section: New safety concerns and reclassification with a submission of an updated RMP.<br>Justification for removal of the safety concern: Conjunctivitis |
| II | SVII.2 | Section: New safety concerns and reclassification with a submission of an updated RMP.<br>Justification for removal of the safety concern: Long-term safety |
| II | SVII.3.1 | The Important potential risk Malignancy is deleted |
| II | SVII.3.1 | The Important potential risk Conjunctivitis is deleted |
| II | SVII.3.2 | The Missing information Long-term safety is deleted |
| II | SVIII.1 | Table 22, Summary of safety concerns: The three safety concerns Malignancy, Conjunctivitis, and Long-term safety have been removed from the table. |
| III | III.2 | Milestone dates of the PASS tralokinumab use in pregnancy and the PASS ECZTEND updated |

| Part | Module | Significant changes made |
|---|---|---|
| V | V.1, V.3 | The three safety concerns Malignancy, Conjunctivitis, and Long-term safety have been removed from the following tables:<br>Table 26, Description of routine risk minimisation measures by safety concern<br>Table 27, Summary table of pharmacovigilance activities and risk minimisation activities by safety concern |
| VI | II.A | List of important risks and missing information: The three safety concerns: Malignancy, Conjunctivitis, and Long-term safety have been removed from the table. |
| VI | II.B | Summary of important risks: The three safety concerns: Malignancy, Conjunctivitis, and Long-term safety have been removed from the table. |
| NA | NA | Annex 3: Updated protocol for PASS tralokinumab use in pregnancy attached. Updated due to changes requested by the FDA during review of the submitted protocol. Changes relate to defining the study population and outcome definitions. |

Other RMP versions under evaluation: Not applicable.

## Risk management plan approval statement

The QPPV has reviewed and approved the RMP by using electronic signature as presented on the last page of this document:

Kira Hammershøi, DVM
QPPV, Global Safety
LEO Pharma A/S

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## List of tables



## List of figures

# Definitions of terms

| | |
|---|---|
| 120-Day Safety Update Report | M5.3.5.3 ISS 120-Day Safety Update Report prepared for the FDA and agreed with EMA to include in the response to CHMP Day 120 List of Questions. |
| ADHAND | Phase 3b, interventional, adaptive, clinical trial to evaluate the efficacy and safety of tralokinumab 300 mg every second week monotherapy compared with placebo in subjects with moderate-to-severe atopic hand eczema who are candidates for systemic therapy (LP0162-2328). |
| AD pool | Data pool including completed tralokinumab trials in subjects with AD: ECZTRA 1, 2, 3, 5 and D2213C00001. AD pool served as the main data source used for evaluating the overall safety profile of tralokinumab in the initial MAA. |
| CAT-354-0703 | Open label parallel-group, bioavailability study to assess the pharmacokinetics of CAT-354 following subcutaneous and intravenous administration |
| Completed trial | Clinical trial with a final clinical report. |
| D2210C00011 | A phase 1 study to evaluate the pharmacokinetics and tolerability of a single SC dose of tralokinumab, when delivered as a 2 mL injection at different flow rates to healthy volunteers |
| D2213C00001 | Tralokinumab dose-finding phase 2b trial in AD |
| ECZTEND | Tralokinumab phase 3 long-term extension trial in subjects with AD who participated in ECZTRA trials (LP0162-1337) |
| ECZTRA 1 | Tralokinumab AD monotherapy trial (LP0162-1325) |
| ECZTRA 2 | Tralokinumab AD monotherapy trial (LP0162-1326) |
| ECZTRA 3 | Tralokinumab AD combination trial where subjects receive tralokinumab in combination with TCS (LP0162-1339) |
| ECZTRA 4 | Tralokinumab phase 1 drug-drug interaction trial in adult subjects with AD (LP0162-1342) |
| ECZTRA 5 | AD vaccine trial where subjects' immune responses to vaccines concomitantly administered with tralokinumab was investigated (LP0162-1341) |
| ECZTRA 6 | Tralokinumab phase 3 trial in adolescent subjects with AD (LP0162-1334) |
| ECZTRA 7 | Tralokinumab phase 3 combination trial in adult subjects with AD inadequately controlled with or having contraindications to oral cyclosporine A, where tralokinumab is given in combination with TCS (LP0162-1346) |
| ECZTRA 8 | Tralokinumab phase 3 AD combination trial where Japanese subjects receive tralokinumab in combination with TCS (LP0162-1343) |
| INJECZTRA | Tralokinumab trial in adult and adolescent subjects with AD by a pre-filled pen (LP0162-1338) |
| M2.7.4 | Summary of clinical safety, tralokinumab in moderate-to-severe atopic dermatitis |
| M5.3.5.3 ISI | Integrated summary of immunogenicity: Tralokinumab in moderate-to-severe atopic dermatitis |
| MI-CP224 | Phase 1, randomized, single-blind, placebo-controlled, single center, single ascending dose in healthy male and female Japanese subjects |
| PK comparability trial | Tralokinumab trial to compare PK of pre-filled pen and pre-filled syringe in healthy subjects (LP0162-1491) |
| TRA-WEI-0015-I | An investigator-initiated study (IIS); phase 2, open-label, single-site, evaluating tralokinumab treatment of AD on skin barrier function |

| | |
|---|---|
| TRAPEDS 1 | Phase 2, single (assessor) blind, randomized, parallel-group, monotherapy trial to evaluate the pharmacokinetics and safety of tralokinumab in children (ages 6 to < 12 years) with moderate to-severe atopic dermatitis (LP0162-1335) |
| TRAPEDS 2 | Phase 3 multi-center trial to evaluate the efficacy and safety of tralokinumab in combination with topical corticosteroids (TCS) in children (ages 2 to <12 years) and infants (age 6 months to <2 years) with moderate-to-severe atopic dermatitis (LP0162-1336) |

# Abbreviations

| | |
|---|---|
| AD | atopic dermatitis |
| ADA | anti-drug antibodies |
| AESI | Adverse event of special interest |
| BSA | body surface area |
| CI | confidence interval |
| CYP | cytochrome P450 |
| EEA | European Economic Area |
| eGFR | estimated glomerular filtration rate |
| EPAR | European Public Assessment Report |
| HF | human factors |
| HPA | hypothalamus-pituitary-adrenal |
| IFU | instructions for use |
| IgE | immunoglobulin E |
| IgG | immunoglobulin G |
| IL | interleukin |
| IMP | investigational medicinal product |
| IV | intravenous |
| LEO Pharma | LEO Pharma A/S |
| MAA | marketing authorisation application |
| mAb | Monoclonal antibody |
| MACE | Major adverse cardiovascular event |
| MedDRA | Medical Dictionary for Regulatory Activities |
| nAb | neutralising anti-drug antibodies |
| NOAEL | no-observed-adverse-effect level |
| PASS | Post-authorisation safety study |
| PDE4 | phosphodiesterase-4 |
| PIL | patient information leaflet |
| PIP | paediatric investigational plan |
| PK | pharmacokinetics |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PSUR | periodic safety update report |
| PYE | Patient-years of exposure |
| PYO | patient-years of observation |
| Q2W | every other week |
| Q4W | every fourth week |
| QT interval | time between the start of the Q wave and the end of the T wave in an electrocardiogram |
| RMP | risk management plan |
| SC | subcutaneous |
| SmPC | summary of product characteristics |
| TCI | topical calcineurin inhibitor(s) |
| TCS | topical corticosteroid(s) |
| TDAR | T cell-dependent antibody response |

| | |
|---|---|
| Th2 | type 2 helper (cells) |
| TSE | transmissible spongiform encephalopathy |
| US | United States |
| UV | Ultraviolet |

# Part I: Product overview

**Table 2 Table Part I.1 – Product Overview**

| | |
|---|---|
| Active substance (INN or common name) | Tralokinumab |
| Pharmacotherapeutic group (ATC Code) | D11AH07: Agents for dermatitis, excluding corticosteroids. Tralokinumab. |
| Marketing Authorisation Applicant | LEO Pharma A/S<br>Industriparken 55<br>DK-2750 Ballerup<br>Denmark |
| Medicinal products to which this RMP refers | Tralokinumab |
| Invented name in the European Economic Area (EEA) | Adtralza® |
| Marketing authorisation procedure | Centralised |
| Brief description of the product | Tralokinumab is a fully human monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4) subclass.<br>Tralokinumab binds specifically to human interleukin 13 (IL-13) and neutralises interactions with the IL-13 receptors.<br>Tralokinumab is manufactured employing the mammalian GS-NS0 expression system. |
| Hyperlink to the Product Information | Link to product information |
| Indication in the EEA | Adtralza® is indicated for the treatment of moderate-to-severe atopic dermatitis in adult and adolescent patients 12 years and older, who are candidates for systemic therapy. |
| Dosage in the EEA | The recommended dose of tralokinumab for adult and adolescent patients 12 years and older is an initial dose of 600 mg (four 150 mg injections given by pre-filled syringes or two 300 mg injections given by pre-filled pen) followed by 300 mg (two 150 mg injections given by pre-filled syringes or one 300 mg injection given by pre-filled pen) administered every other week as subcutaneous injection. |

| | |
|---|---|
| | At prescriber's discretion, every fourth week dosing may be considered for patients who achieve clear or almost clear skin after 16 weeks of treatment. The probability of maintaining clear or almost clear skin may be lower with every fourth week dosing. |
| Pharmaceutical form and strengths | Pre-filled syringe containing150 mg tralokinumab in 1 mL (150mg/mL) solution in a single injection.<br>Pre-filled pen containing 300 mg tralokinumab in 2.0 mL (150mg/mL) in a single injection |
| Is/will the product be subject to additional monitoring in the EU? | Yes |

# Part II: Safety specification

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

### Introduction

Atopic dermatitis (AD) is the most common inflammatory skin disease in the developed world (1). AD is a chronic inflammatory skin disorder, and the course of the disease may be continuous over many years or be characterised by periods of remission and episodical relapses (2). Disease symptoms in moderate-to-severe AD include intense itch, xerosis, and recurrent eczematous skin lesions. These symptoms have a significant impact on patients' morbidity, quality of life, psychological well-being, and work productivity. On a global population level, AD is ranked as the most impactful skin disease, leading to a significant burden of disease over many years (3, 4).

### Incidence

The onset of disease is usually reported in childhood, but the prevalence in adults remains high despite some tendency to remission. It is notable however that approximately 1 in 4 adults with AD reports onset of disease in adulthood (5). The incidence of AD peaks in infancy, with an onset before 6 years of age in approximately 80% of patients (1, 6). A study of Danish and Swedish children born between 1997 and 2011 found an AD incidence of 48.7 per 1,000 person years in infants (<1 year) (7). A similar study of Norwegian children found that the incidence of AD amongst infants increased from 52 per 1,000 person years in 2009 to 73 per 1,000 person years in 2015 (8). In a cohort study where 1501 randomly selected Danish schoolchildren were followed for 15 years, an AD incidence of 8.9 per 1,000 person years was found between the ages of 14 to 29 years (9).

**Prevalence**

The prevalence of AD is highest in childhood and may be as high as 25%. While most childhood AD cases resolve before adulthood (10), the prevalence remains high in adults and varies between regions. In a web-based survey using a modified UK Working Party definition of AD, the 1-year prevalence of AD in adults was reported to be 4.3 % in Japan, 8.1% in Canada, 9.4% in Europe, and 11.9% in the US (11). In a similar web-based survey that used data from the US Census Bureau to create sample weights adjusting for age, sex, race, ethnicity, education level, census region, income, home ownership status and metropolitan area, the 1-year prevalence of AD representative for the adult US population was estimated to be 7.3% (12).

**Demographics of the population in the proposed indication – age, gender, and racial origin**

The prevalence among adults has been estimated to be around 10%, with a similar prevalence across age groups (13). Most studies suggest that a slightly higher proportion of patients with AD are female (13-16). A lower prevalence of AD has been found in Black or African American patients compared with White patients, whereas a higher prevalence of AD was found in other/multiracial patients compared with White patients (13).

**Risk factors for the disease**

AD belongs to a group of disorders commonly referred to as atopic disease, which includes asthma, allergic rhinitis, and atopic dermatitis. Atopic disease is typically associated with a heightened IgE-mediated immune response to common allergens, especially inhaled allergens and food allergens. The strongest risk factor for developing AD is a family history of atopic disease, particularly AD, and twin studies suggest a high heritability of AD (17). The risk of developing AD increases 1.5-fold if atopic disease is present in one parent, whereas the risk is increased approximately 3-fold if one parent has AD and approximately 5-fold if both parents have AD (18, 19). Other well-established risk factors include living in urban areas, low UV light exposure, dry climatic conditions, high consumption of sugars and polyunsaturated fats, repeated exposure to antibiotics before 5 years of age, a small family size, and living in a house with a high education level (20).

Concordance data from twin studies indicate that the heritability of AD may be as high as 75% (17), and 34 genomic regions harbouring potential AD susceptibility genes have been identified (1). The AD-associated genomic regions are enriched in genes encoding structural molecules and genes involved in innate immune signalling, T cell activation and Th2 cell differentiation. The strongest known genetic risk factor for AD is semi-dominant mutations in the *FLG* gene, encoding the filaggrin protein, which is involved in terminal epidermal

differentiation and aggregation of keratin intermediate filaments (21). The potential AD susceptibility genes involved in Th2 cell differentiation include the *IL13* gene, encoding IL-13 (1).

**The main existing treatment options**

Management of moderate-to-severe AD is challenging because of the chronicity of the disease and the limited therapeutic options that are both efficacious and have an acceptable long-term safety profile. A 'control-based' and 'risk-based' model of disease management in which an initial diagnosis is followed by treatment according to categorisation of severity is usually recommended.

Treatment guidelines suggest a basic (lifestyle) therapy including educational programmes, emollients, bath oils, and avoidance of clinically relevant allergens and irritants (22-24). When basic therapy is insufficient to achieve disease control, additional AD treatments should be administered in conjunction. The pharmacological treatment algorithm for AD progresses from mild topical anti-inflammatory therapy to high potency topical therapy, and in some cases leads to systemic immunomodulatory therapy. In general, the key treatment guidelines recommend the use of systemic treatment in patients that are refractory to optimised topical therapies (22, 23, 25, 26).

Topical anti-inflammatory treatments and UV therapy are the first line of treatment on top of the basic therapy. The topical treatments typically consist of topical corticosteroids (TCS) and/or topical calcineurin inhibitors (TCI) (23, 27, 28). Furthermore, topical PDE4 inhibitors have been approved in some countries to treat mild-to-moderate AD (29). Recently a topical JAK inhibitor, delgocitinib, has been approved in EU to treat chronic hand eczema, which is a specific type of AD (30).

TCS are available in different concentrations and potencies and are used as the first-line pharmaceutical intervention. TCS are sufficient to treat flares of patients with mild AD and some with moderate AD. However, for many of the patients with moderate-to-severe AD, high potency TCS may not be enough to achieve disease control or may be inappropriate from both a practical and a safety point of view. High potency TCS can cause local side effects like skin atrophy (which can be permanent), hypertrichosis, dyspigmentation, and acne. Systemic side effects can occur when a large body surface area (BSA) is treated with TCS; these include hypothalamus-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, decreased glucose tolerance, osteoporosis and cataracts (31).

TCI, such as tacrolimus and pimecrolimus, have efficacy comparable to medium potency TCS, but TCI can be preferred over TCS due to side effects such as skin atrophy and acne. Due to the lower efficacy, use of TCI is often limited to skin areas where use of TCS is considered inappropriate, including face, neck, and skinfolds (32).

Topical phosphodiesterase-4 (PDE4) inhibitors are well tolerated but are only approved for mild-to-moderate disease. Topical PDE4 inhibitors may cause allergic reactions, which can be serious and may include hives, itching, swelling, and redness. The most common side effect is application site pain. Topical PDE4 inhibitors, or a low dose TCS and/or a TCI, may be used for long-term maintenance therapy following TCS treatment of symptom exacerbations (32).

Phototherapy (broad-band UVB, narrow-band UVB, or long wave UVA) can be used in combination with basic therapy and topicals, especially when topicals are not sufficient or inconvenient due to a large affected BSA. Phototherapy can be effective in moderate-to-severe AD, but it is time consuming, requires specialist treatment in clinics, the onset of action is slow, and side effects like skin burns and skin malignancies limit long-term use and repeat courses (23, 26, 33).

Systemic therapy is recommended on top of basic therapy when topical anti-inflammatory therapies are either inadequate or inappropriate. Systemic therapy should be used together with TCS as needed on lesional skin unless TCS is contraindicated. Commonly used non-selective immunosuppressive systemic therapies for AD include systemic corticosteroids, cyclosporine, methotrexate, azathioprine and mycophenolate mofetil. Especially when used long-term, these are associated with toxicities (23, 26, 33). The only other selective immunomodulating biologic monoclonal antibodies (mAb) therapies currently available for the treatment of AD are dupilumab approved in 2017 (25, 26, 34) and Lebrikizumab approved in November 2023 (35).

Short-term treatment with oral corticosteroids is used as an option to treat flares, but restrictive use is recommended due to side effects, which includes increased blood pressure, disturbed mental health, increased susceptibility to infections, osteoporosis, decreased glucose tolerance, HPA-axis suppression, Cushing’s syndrome, cataracts and glaucoma. Long-term treatment with systemic corticosteroids is therefore not recommended (36).

Oral cyclosporine is licensed in many European countries for the treatment of patients with AD who cannot achieve adequate disease control on topical therapy. Cyclosporine is usually effective, but the dose-dependent side effects like nephrotoxicity, hypertension, and the risk of UV-induced skin cancer and other malignancies limit the long-term use (37).

Methotrexate, azathioprine, and mycophenolate mofetil are all immunosuppressants used off-label for treatment of AD. All 3 therapies are somewhat efficacious and can be used long-term if tolerated. The list of side effects includes hepatotoxicity, bone marrow suppression, nausea and diarrhoea. Methotrexate has immunosuppresive properties and photosensitising properties which both increase the risk of skin cancers (38).

Azathioprine causes an increased risk of non-melanoma skin cancer and lymphoma when used long-term in inflammatory bowel disease, and this warrants restriction for the use in AD (26).

Compared to systemic immunomodulating agents (e.g., cyclosporine, methotrexate and azathioprine), biologic therapy with mAbs offers a more selective treatment by targeting specific molecules involved in the AD pathogenesis. The targeted IL-13 pathway with tralokinumab differentiates it from dupilumab, in that dupilumab targets both the IL-4 and the IL-13 pathway. Tralokinumab binds specifically to human interleukin 13 (IL-13) and neutralises interactions with the IL-13 receptors (IL-13Rα1/IL-4Rα receptor complex). IL-13 is a major driver of human type 2 inflammatory disease, such as AD, and inhibiting the IL-13 pathway with tralokinumab decreases many of the mediators of type 2 inflammation. A third mAb, lebrikizumab was recently approved to treat moderate to severe AD and binds to IL-13 and inhibits it by preventing its signalling through the IL-4 receptor alpha.

**Natural history of AD in the untreated population, including mortality and morbidity**
AD may worsen if left untreated, leading to increase in the affected BSA and exacerbations of erythema, itch, xerosis, and cracking and oozing of AD lesions. In severe cases, disease exacerbation can lead to a systemic reaction which requires hospitalisation to regain disease control.

Skin infections are a major complication for patients with moderate-to-severe AD. 80–100% of patients with AD are colonised with *Staphylococcus aureus* on active lesions, whereas only 5–30% of people with normal skin are colonised with *S. aureus* (39). Cracking of lesions disrupts the natural skin barrier, which may lead to *S. aureus* skin infections (impetigo and cellulitis) and worsening of AD (40, 41). Viral infections (herpes simplex and pox virus) are also more common in patients with AD. Eczema herpeticum is a severe widespread infection of herpes simplex virus which is mainly seen in severely affected patients with AD (40, 42).

On a global population level, AD is ranked as the most impactful skin disease, leading to a significant burden of disease over many years (3, 4). The symptoms of AD can be debilitating and associated with pain, sleep disturbance, and impaired social functioning (12). In the

Global Burden of Disease Study 2013, skin diseases were the fourth largest cause of disability worldwide and dermatitis, including AD, was the most burdensome skin disease (43). The patient burden of disease relates directly to the physical signs and symptoms of disease (e.g., pruritus and pain) as well as indirectly to the harmful impact of skin symptoms on sleep (e.g., difficulty falling asleep, more frequent awakenings, prolonged awakenings and fragmented sleep), mental health, concentration, physical activity and sedentary behaviour, activities of daily living, performance at school and work, increased sick days and missed days of work (29, 44).

Mortality in patients with AD has not been extensively studied, but one study investigated the 10-year mortality in patients hospitalised for AD, which indicates that the majority of this population had severe AD. This study found a 71% increase in 10-year mortality in patients hospitalised for AD compared with an age- and sex-matched control population, and found that patients with AD on average died 8.3 years younger than the control population (45).

**Important comorbidities and complications**

IgE-mediated sensitisation to common allergens is frequent in patients with AD, especially those with severe disease (46). The most common comorbidities of AD are asthma and allergic rhinitis, which occurs in 25–33% of patients with AD (13, 47, 48). The prevalence of food allergy in the adult AD population is approximately 10% (49).

Patients with AD are at an increased risk of developing cardiovascular disease, and the risk of cardiovascular disease increase with the severity of AD (50). Patients with severe AD have a 20% increased risk of stroke; 40–50% increased risk of myocardial infarction, unstable angina, atrial fibrillation, and cardiovascular death, and a 70% increased risk of heart failure (50).

AD is associated with neuropsychiatric disorders including depression, anxiety, and suicidal ideation (50-54), and more than half of patients with moderate-to-severe AD have been reported to suffer from depression and anxiety (55).

# Part II: Module SII – Non-clinical part of the safety specification

**Table 3 Key safety findings from non-clinical studies**

| **Toxicity** |
|---|
| *Key issues identified from acute or repeat-dose toxicity studies:*<br>No tralokinumab-related effects were detected in intravenous (IV) repeat-dose toxicity studies in cynomolgus monkeys of up to 6 months duration at doses up to 100 mg/kg/week (study 509615) or in subcutaneous (SC) repeat-dose toxicity studies up to 13 weeks at doses up to 300 mg/animal/week (study 514981). The highest dose was the no-observed-adverse-effect level (NOAEL) in all repeat-dose studies.<br><br>No adverse effects of tralokinumab on immune function were detected in any study, including assessment by immunophenotyping (in 6-month study and pre-and postnatal development, study 20054081), T cell-dependent antibody response (TDAR) assay (in repeat-dose studies in sexually mature animals and in pre- and postnatal; study 20054081), and haematology and histopathological evaluation of organs of the immune system (repeat and reproduction toxicity studies). |
| *Reproductive/developmental toxicity:*<br>No effects on reproductive organs or sperm parameters were detected in sexually mature cynomolgus monkeys dosed with tralokinumab SC up to 350 mg/animal/week (females) or 600 mg/animal/week (males) (studies 2843-005 and 2843-006).<br><br>In the enhanced pre-postnatal development studies in the cynomolgus monkey at up to 100 mg/kg/week IV (studies SNBL.200.15 and 20054081), no effects on pregnancy were observed, and there were no infant growth or developmental adverse effects (including on infant immune function assessed with a TDAR assay and immunophenotyping) through 6 months postpartum. The developmental and maternal NOAEL was 100 mg/kg. |
| **Safety pharmacology** |
| *Cardiovascular system, including potential effect on the QT interval:*<br>No effects were detected of tralokinumab on the cardiovascular system assessed by blood pressure and electrocardiogram evaluation in cynomolgus monkey repeat-dose toxicity studies. |
| **Other toxicity-related information or data** |
| No binding of tralokinumab to normal human tissues was detected in an in vitro tissue cross-reactivity study. |

**Table 4 Conclusions on non-clinical data**

| Safety concerns from non-clinical data | |
|---|---|
| Important identified risks (confirmed by clinical data): | None |
| Important potential risks (not refuted by clinical data or which are of unknown significance): | None |
| Missing information: | None |

# Part II: Module SIII – Clinical trial exposure

## Data lock point used in this RMP

The data lock point for this RMP, version 3.0, was 31-Oct-2024.

## Introduction to the tralokinumab clinical development programme

AstraZeneca was the original sponsor of the tralokinumab development programme, but in 2016, LEO Pharma acquired the global licence to develop tralokinumab within dermatology.

**Figure 1 Tralokinumab development programme in Atopic Dermatitis**

| Phase 1 | Phase 2 | Phase 3 |
|---|---|---|
| D2210C00011* | D2213C00001 | ECZTRA 1 |
| MI-CP224* | ECZTRA 5 | ECZTRA 2 |
| CAT-354-0703* | TRAPEDS 1** | ECZTRA 3 |
| | | ECZTRA 6 |
| ECZTRA 4 | | ECZTRA 7 |
| | | ECZTRA 8 |
| | | PK-Comparability trial*** |
| | | ECZTEND |
| | | INJECZTRA |
| | | TRAPEDS 2** |
| | | ADHAND** |

*All healthy subjects ** Currently on-going *** Comparison of PK of pre-filled pen and pre-filled syringe in healthy subjects

At the time of the Data Lock Point (DLP) for this Risk Management Plan, the clinical development programme in AD is comprised of:18 clinical trials, 4 of which were in healthy volunteers, 14 in patients with AD, 3 of which are ongoing.

Since the DLP of the previous RMP, the following trials have been completed:

- ECZTEND
- INJECZTRA

At the time of DLP of this RMP, the following clinical trials were ongoing:

- TRAPEDS 1
- TRAPEDS 2
- ADHAND

**Presentation of trial designs of the completed clinical trials in AD**

**ECZTRA 1 and 2** were randomised, double-blind, placebo-controlled, phase 3 trials to evaluate the efficacy and safety of tralokinumab monotherapy in adults with moderate-to-severe AD. In the initial treatment period (from Week 0 to Week 16), subjects were randomised in a 3:1 ratio to 300 mg tralokinumab every other week (Q2W) or placebo Q2W. All subjects randomised to tralokinumab received a loading dose of 600 mg. Subjects who achieved a clinical response at Week 16 were transferred to the maintenance period (from Week 16 to Week 52). Responders from the tralokinumab group were re-randomised 2:2:1 to tralokinumab 300 mg Q2W, tralokinumab every fourth week (Q4W, alternating tralokinumab 300 mg and placebo Q2W), or placebo Q2W. Responders from the placebo group continued to receive placebo. Subjects that did not achieve a clinical response at Week 16 or did not maintain a clinical response after Week 16 were transferred to open-label treatment until Week 52 (until Week 68 in Japan due to a request from the PMDA). All subjects in open-label treatment received tralokinumab 300 mg Q2W in combination with optional TCS, as needed. All subjects, except those who enter the long-term extension trial, ECZTEND, enter an off-treatment safety follow-up period (for 16 weeks after last dose of IMP).

**ECZTRA 3** was a randomised, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of tralokinumab in combination with TCS in adults with moderate-to-severe AD. In this trial, subjects were to apply a thin film of supplied TCS (mometasone furoate, 0.1% cream) on active lesions as needed. In the initial treatment period (from Week 0 to Week 16), subjects were randomised in a 2:1 ratio to tralokinumab 300 mg Q2W + TCS or placebo Q2W + TCS. All subjects randomised to tralokinumab received a loading dose of 600 mg. In the continuation treatment period (from Week 16 to Week 32), responders from the tralokinumab + TCS group at Week 16 were re-randomised 1:1 to tralokinumab 300 mg + TCS Q2W or tralokinumab Q4W + TCS (alternating tralokinumab 300 mg and placebo Q2W in combination with TCS). Responders from the placebo + TCS group at Week 16 continued

with placebo. Subjects that did not achieve clinical response at Week 16 were allocated to tralokinumab 300 mg Q2W + TCS, regardless of prior treatment. All subjects, except those who enter the long-term extension trial, ECZTEND, enter an off-treatment safety follow-up period (for 16 weeks after last dose of IMP).

**ECZTRA 4** was an open-label drug-drug interaction trial to investigate the effects of tralokinumab on the pharmacokinetics (PK) of selected cytochrome P450 (CYP) substrates (caffeine, warfarin, omeprazole, metoprolol, and midazolam) in adult subjects with moderate-to-severe AD. The trial consisted of a 1-week pre-IMP period and a 16-week treatment period. A cocktail containing 5 CYP substrates was administered on Day -7 (pre-IMP period), on Day 8, and at Week 15. All subjects were also dosed with tralokinumab 600 mg (4 injections; loading dose) on Day 1, followed by tralokinumab 300 mg Q2W, with the last dose of IMP at Week 14. All subjects, except those who enter the long-term extension trial, ECZTEND, entered an off-treatment safety follow-up period (for 16 weeks after last dose of IMP).

**ECZTRA 5** was a randomised, double-blind, placebo-controlled phase 2 trial to evaluate the effect of tralokinumab on vaccine antibody responses in adults with moderate-to-severe AD. In the 16-week treatment period, subjects were randomised in a 1:1 ratio to tralokinumab 300 mg Q2W or placebo Q2W. All subjects randomised to tralokinumab received a loading dose of 600 mg. At Week 12, all subjects received 2 vaccines, a meningococcal vaccine and a combined tetanus, diphtheria, and acellular pertussis vaccine. All subjects, except those who entered the long-term extension trial, ECZTEND, entered an off-treatment safety follow-up period (for 16 weeks after last dose of IMP).

**ECZTRA 6** was a phase 3, randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of tralokinumab in adolescent subjects aged 12 to <18 years with moderate-to-severe AD. As for ECZTRA 1 and 2, the trial consisted of an initial treatment period of 16 weeks, and a maintenance treatment period of 36 weeks. Subjects were randomised 1:1:1 to either tralokinumab 150 mg Q2W, tralokinumab 300 mg Q2W, or placebo Q2W. At randomisation, subjects in the tralokinumab 300 mg arm received a loading dose of 600 mg, whereas subjects in the tralokinumab 150 mg arm received a loading dose of 300 mg. Subjects who achieved a clinical response at Week 16 were transferred to the maintenance period (from Week 16 to Week 52). Subjects with a clinical response from the tralokinumab 300 mg arm were re-randomised 1:1 to tralokinumab 300 mg Q2W or Q4W until Week 52, whereas subjects with a clinical response from the tralokinumab 150 mg arm were re-randomised 1:1 to tralokinumab 150 mg Q2W or Q4W until Week 52. Responders from the placebo group continued to receive placebo. Subjects that did not achieve a clinical response at Week 16 or did not maintain a clinical response after Week 16 were transferred to

open-label treatment until Week 52, if considered appropriate by the investigator. All subjects in open-label treatment received tralokinumab 300 mg Q2W in combination with optional TCS, as needed. All subjects, except those who entered the long-term extension trial, ECZTEND, entered an off-treatment safety follow-up period (for 16 weeks after last dose of IMP).

**ECZTRA 7** was a phase 3, randomised, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of tralokinumab in combination with TCS in adults with moderate-to-severe AD who were not adequately controlled with or had contraindications to cyclosporine A. The trial consisted of a 2- to 6-week screening period and a 26-week treatment period. Subjects were randomised 1:1 to either tralokinumab 300 mg Q2W + TCS or placebo Q2W + TCS. All subjects randomised to tralokinumab received a loading dose of 600 mg. All subjects, except those who entered the long-term extension trial, ECZTEND, entered an off-treatment safety follow-up period (for 16 weeks after last dose of IMP).

**ECZTRA 8** was a randomised, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of tralokinumab in combination with TCS in adult Japanese subjects with moderate-to-severe AD. In this trial, subjects were to apply a thin film of supplied TCS (mometasone furoate, 0.1% cream) on active lesions as needed. The trial consisted of a 2- to 6-week screening period and a 16-week treatment period. Subjects were randomised in a 1:1 ratio to tralokinumab 300 mg Q2W + TCS or placebo Q2W + TCS. All subjects randomised to tralokinumab received a loading dose of 600 mg. All subjects, except those who entered the long-term extension trial, ECZTEND, entered an off-treatment safety follow-up period (for 6 weeks after last dose of IMP).

**D2213C00001** was a randomised, double-blind, placebo-controlled, dose-ranging phase 2b trial in adults with moderate-to-severe AD. In the 12-week treatment period, subjects were randomised 1:1:1:1 to 45 mg tralokinumab, 150 mg tralokinumab, 300 mg tralokinumab, or placebo. All subjects were treated with mid-strength TCS throughout the trial. All subjects entered an off-treatment safety follow-up period (for 12 weeks after last dose of IMP).

**PK Comparability Trial** was a single centre, randomized, open-label, 2-period, 2 sequence cross-over trial designed to compare the PK and to evaluate the safety, tolerability, and immunogenicity of 300 mg tralokinumab administered as a 1 × 2 mL SC injection with the pre-filled pen versus 2 × 1 mL consecutive subcutaneous injections with the pre-filled syringe in healthy subjects. Subjects were randomized to 1 of 2 treatment sequences (pre-filled pen + pre-filled syringe or pre-filled syringe + pre-filled pen) in a 1:1 ratio. The trial consisted of a screening visit between days -22 and -2, followed by two 16-week treatment periods. IMP

was administered on day 1 of each period, and the two treatment periods were separated by a 2-week washout period, so that the doses in the two treatment periods were separated by at least 18 weeks. A safety follow-up visit (end-of-trial visit) took place 16 weeks after last IMP administration.

**ECZTEND** was an open-label phase 3 extension trial investigating the long-term safety and efficacy of tralokinumab in subjects who previously participated in ECZTRA trials (called the parent trials) or the investigator-initiated trial (IIS; TRA-WEI-0015-I [see Definitions of terms for details in this IIS]). ECZTEND was listed as an additional pharmacovigilance activity for Adtralza® in this RMP. The ECZTEND trial included a 2-week screening period, which was expected to overlap with the safety follow-up period of the parent trials (although this did not always happen) and consisted of a long-term treatment period of up to 5 years. Thereafter, an off-treatment safety follow-up period was conducted (for 4 weeks after last dose of IMP, except for subjects from the parent trial ECZTRA 6 in adolescents with AD, where the duration of the safety follow-up period was 16 weeks after last dose of IMP).

**INJECZTRA** was an open-label, single-arm, phase 3 trial, in adult and adolescent subjects with moderate-to-severe atopic dermatitis. The trial was designed to evaluate the efficacy and safety of tralokinumab when administered by a pre-filled pen. The trial consisted of a 2-to-4-week screening period (depending on the need for wash-out of disallowed medications), a 16-week treatment period, and a 4-week safety follow-up period. At the baseline visit, eligible subjects received an initial loading dose of subcutaneous tralokinumab 600 mg. This dose was administered with the use of 2 pre-filled pens containing 300 mg/2 mL each. During the administration of the initial loading dose, subjects were trained on the usage of the pre-filled pen. For the rest of the treatment period, all subjects self-administered a dose of 300 mg tralokinumab Q2W (2 mL). The IMP was administered every other week during the treatment period, and the last IMP administration occurred at Week 14. All completing subjects had safety follow-up assessments 6 weeks after the last IMP administration.

**Presentation of the trial design in ongoing clinical trials in AD**

**TRAPEDS 1** Pharmacokinetics in Children

LP0162-1335 / TRAPEDS 1 is an ongoing single (assessor) blinded, randomized, parallel-group, monotherapy phase 2 trial to evaluate the pharmacokinetics and safety of tralokinumab in children (age 6 to <12 years) with moderate to-severe atopic dermatitis. The trial consists of a 2–6-week screening period, a 16-week initial treatment period, a 52-week open label treatment period, a long-term extension treatment period for up to 106 weeks (until a global end-of-treatment visit on approximately 15-Jan-2026), and a 14-week safety follow-up period. 28 subjects aged 6 to <12 years were randomized 1:1 to treatment with either a low fixed dose

(13 subjects) or a high fixed dose (15 subjects) of tralokinumab, depending on their weight at baseline. Currently, the remaining 22 subjects have progressed to the long-term extension treatment period.

**TRAPEDS 2** Efficacy and Safety in Children
LP0162-1336 / TRAPEDS 2 is an ongoing phase 3 multi-center trial to evaluate the efficacy and safety of tralokinumab in combination with topical corticosteroids (TCS) in children (age 2 to <12 years) and infants (age 6 months to <2 years) with moderate-to- severe atopic dermatitis. The trial is randomized, double-blind, placebo-controlled, and parallel-group for children (age 2 to <12 years) and open-label and single-group for infants (age 6 months to <2 years). Dose and dosing frequency of tralokinumab for each subject will depend on the subject's body weight. At least 183 subjects aged 2 to <12 years will be randomized 2:1 to treatment with tralokinumab+TCS or placebo+TCS. Approximately 12 subjects aged 6 months to <2 years will be assigned to open-label treatment with tralokinumab+TCS. These subjects will only be enrolled in the US and Canada.

**ADHAND** Efficacy and Safety in subjects with moderate-to-severe atopic hand eczema
LP0162-2328 (ADHAND) is a phase 3b, interventional, adaptive, clinical trial to evaluate the efficacy and safety of tralokinumab 300 mg every second week monotherapy compared with placebo in subjects with moderate-to-severe atopic hand eczema who are candidates for systemic therapy. The trial consists of a 1-4 week screening period, 16-week double-blind placebo-controlled treatment period, then a 16-week open-label period where all subjects receive 300 mg tralokinumab every 2 weeks followed by a 4 week safety follow-up period. Subjects are randomized 2:1 to tralokinumab and placebo and a minimum of 204 subjects will be randomized. An interim sample size evaluation will determine the final sample size. As of 31 Oct 2024 a total of 198 subjects were randomized in the ADHAND trial. However, subjects are randomised 2:1, but all who persist in the trial will enter open-label after week 16.

**Exposure to tralokinumab across all indications in completed clinical trials**
Across all indications, 5339 subjects received at least one dose of tralokinumab, including subjects who were initially randomised to placebo and subsequently allocated to treatment with tralokinumab. Exposure by indication in completed clinical trials is presented in Table 5.

**Table 5 Exposure to tralokinumab (all doses) in completed clinical trials, all indications**

| Indication | Number of subjects exposed to tralokinumab |
|---|---|
| Healthy subjects | 219 |
| Atopic dermatitis | 3045 |
| Asthma | 1888 |
| Ulcerative colitis | 55 |
| Idiopathic pulmonary fibrosis | 132 |
| **Total** | **5339** |

N: Number of subjects with observation. PYE: Patient years of exposure.
18NOV2024-/leo/clinical/lp0162/rmp/rmp2024/tfl/programs/t_ad_exp_exp_indic.sas-t_10010_ad_exp_byindic.txt

**Exposure to tralokinumab in completed clinical trials in AD**

The vast majority of the exposure to tralokinumab in AD (96.3%) was with the 300 mg tralokinumab dose, which is the marketed dose. To focus the exposure in AD on the dose, exposure by duration (Table 6 and Table 7), exposure by age (Table 8 and Table 9), and exposure by race (Table 10 and Table 11) below include subjects exposed to the 150 mg and 300 mg doses of tralokinumab.

For completeness, data from AD subjects exposed to the 45 mg, 150 mg and 300 mg doses of tralokinumab are included in the exposure by dose (Table 12).

**Table 6 Duration of exposure to tralokinumab 300 mg in completed AD clinical trials**

| Duration of exposure (atopic dermatitis indication) | Subjects | Patient-years |
|---|---|---|
| ≥ 0 weeks | 2932 | 6201 |
| ≥ 8 weeks | 2839 | 6195 |
| ≥ 12 weeks | 2783 | 6185 |
| ≥ 16 weeks | 2674 | 6159 |
| ≥ 20 weeks | 2449 | 6088 |
| ≥ 24 weeks | 2390 | 6065 |
| ≥ 28 weeks | 2327 | 6035 |

| Duration of exposure (atopic dermatitis indication) | Subjects | Patient-years |
|---|---|---|
| ≥ 32 weeks | 2257 | 5996 |
| ≥ 36 weeks | 2161 | 5936 |
| ≥ 40 weeks | 1981 | 5811 |
| ≥ 44 weeks | 1942 | 5780 |
| ≥ 48 weeks | 1906 | 5750 |
| ≥ 52 weeks | 1868 | 5714 |
| >= 2 years | 1325 | 5058 |
| >= 3 years | 966 | 4153 |
| >= 4 years | 577 | 2804 |
| >= 5 years | 225 | 1234 |
| >= 6 years | 19 | 115 |

Note:
A subject is counted in both treatment doses of 150 mg and 300 mg, if a subject switches from one dose to another during the trial
19DEC2024-/leo/clinical/lp0162/rmp/rmp2024/tfl/programs/t_ad_expos_cum_sum.sas-t_10020_ad_exp300_cum_sum.txt

**Table 7 Duration of exposure to tralokinumab 150 mg in completed AD clinical trials**

| Duration of exposure (atopic dermatitis indication) | Subjects | Patient-years |
|---|---|---|
| ≥ 0 weeks | 150 | 53.7 |
| ≥ 8 weeks | 143 | 53.2 |
| ≥ 12 weeks | 138 | 52.4 |
| ≥ 16 weeks | 93 | 41.8 |
| ≥ 20 weeks | 26 | 21.0 |
| ≥ 24 weeks | 21 | 19.0 |
| ≥ 28 weeks | 21 | 19.0 |
| ≥ 32 weeks | 17 | 16.8 |
| ≥ 36 weeks | 17 | 16.8 |
| ≥ 40 weeks | 17 | 16.8 |
| ≥ 44 weeks | 16 | 16.0 |
| ≥ 48 weeks | 16 | 16.0 |
| ≥ 52 weeks | 16 | 16.0 |

Note: A subject is counted in both treatment doses of 150 mg and 300 mg, if a subject switches from one dose to another during the trial.
18NOV2024-/leo/clinical/lp0162/rmp/rmp2024/tfl/programs/t_ad_expos_cum_sum.sas-t_10030_ad_exp150_cum_sum.txt

**Table 8 Exposure to tralokinumab 300 mg by age group and gender in completed AD clinical trials**

| Age group (atopic dermatitis indication) | Subjects | | | Patient-years | | |
|---|---|---|---|---|---|---|
| | M | F | Total | M | F | Total |
| 12-14 years | 62 | 73 | **135** | 71.0 | 80.1 | **151.1** |
| 15-17 years | 99 | 89 | **188** | 124.2 | 102.5 | **226.7** |
| 18–64 years | 1438 | 1078 | **2516** | 3281.1 | 2307.5 | **5588.6** |
| ≥65 years | 83 | 55 | **138** | 148.0 | 86.7 | **234.8** |
| **Total** | **1682** | **1295** | **2977** | **3624.3** | **2576.8** | **6201.2** |

Includes all exposure time(i.e. excluding safety follow-up) from all completed trials (300mg).
Note: A subject is counted in both treatment doses of 150 mg and 300 mg,if a subject switches from one dose to another during the trial. Subjects who entered ECZTEND could be

included in more than one age group.
18NOV2024-/leo/clinical/lp0162/rmp/rmp2024/tfl/programs/t_rmp_ex_dur.sas-t_10040_ad_exp300_dur age_sex.txt

**Table 9 Exposure to tralokinumab 150 mg by age group and gender in completed AD clinical trials**

| Age group (atopic dermatitis indication) | Subjects | | | Patient-years | | |
|---|---|---|---|---|---|---|
| | M | F | Total | M | F | Total |
| 12-14 years | 19 | 20 | 39 | 9.9 | 9.1 | 19.0 |
| 15-17 years | 32 | 28 | 60 | 12.6 | 11.0 | 23.6 |
| 18–64 years | 25 | 25 | 50 | 5.5 | 5.5 | 11.0 |
| ≥65 years | 1 | - | 1 | 0.2 | - | 0.2 |
| **Total** | **77** | **73** | **150** | **28.2** | **25.6** | **53.8** |

Includes all exposure time
(i.e., excluding safety follow-up) from all completed trials (150mg).
Note: A subject is counted in both treatment doses of 150 mg and 300 mg, if a subject switches from one dose to another during the trial.
Subjects who entered ECZTEND could be included in more than one age group.

18NOV2024-/leo/clinical/lp0162/rmp/rmp2024/tfl/programs/t_rmp_ex_dur.sas-t_10050_ad_exp150_dur _age_sex.txt

**Table 10 Exposure to tralokinumab 300 mg by race in completed AD clinical trials**

| Race (atopic dermatitis indication) | Subjects | Patient-years |
|---|---|---|
| White | 1961 | 4362.3 |
| Black or African American | 263 | 374.5 |
| Asian | 605 | 1274.7 |
| Native Hawaiian or Other Pacific Islander | 12 | 15.4 |
| American Indian or Alaska Native | 6 | 10.4 |
| Multiple | 1 | 0.3 |
| Other | 71 | 147.6 |
| Missing | 13 | 16.1 |
| **Total** | **2932** | **6201.1** |

Includes all exposure time(i.e., excluding safety follow-up) from all completed trials (300mg).
Note: A subject is counted in both treatment doses of 150 mg and 300 mg, if a subject switches from one dose to another during the trial. For the subjects who entered ECZTEND, race is presented as collected from ECZTEND.
18NOV2024-/leo/clinical/lp0162/rmp/rmp2024/tfl/programs/t_rmp_ex_dur.sas-t_10060_ad_exp300_dur_race.txt

**Table 11 Exposure to tralokinumab 150 mg by race in completed AD clinical trials**

| Race (atopic dermatitis indication) | Subjects | Patient-years |
|---|---|---|
| White | 89 | 31.2 |
| Black or African American | 18 | 5.5 |
| Asian | 36 | 13.8 |
| Native Hawaiian or Other Pacific Islander | - | - |
| American Indian or Alaska Native | 1 | 0.3 |
| Multiple | - | - |
| Other | 3 | 2.1 |
| Missing | 3 | 0.9 |
| **Total** | **150** | **53.7** |

Includes all exposure time
(i.e., excluding safety follow-up) from all completed trials (150mg).
Note: A subject is counted in both treatment doses of 150 mg and 300 mg, if a subject switches from one dose to another during the trial. For the subjects who entered ECZTEND, race is presented as collected from ECZTEND.18NOV2024-/leo/clinical/lp0162/rmp/rmp2024/tfl/programs/t_rmp_ex_dur.sas-t_10070_ad_exp150_dur_race.txt

**Table 12 Exposure by dose in completed AD clinical trials**

| Dose of exposure (atopic dermatitis indication) | Subjects | Patient-years |
|---|---|---|
| 45 mg tralokinumab | 50 | 10.8 |
| 150 mg tralokinumab | 150 | 53.7 |
| 300 mg tralokinumab | 2932 | 6201.1 |
| **Total** | **3045** | **6265.7** |

Includes all exposure time
(i.e., excluding safety follow-up) from completed trials (all doses).
Note: A subject is counted in both treatment doses of 150 mg and 300 mg, if a subject switches from one dose to another during the trial. * Studies included: LP0162-1325, LP0162-1326, LP0162-1334, LP0162-1339, LP0162-1341, LP0162-1342, LP0162-1343, LP0162-1346, LP0162-1338, LP0162-1337 and D2213C00001 (all doses)
18NOV2024-/leo/clinical/lp0162/rmp/rmp2024/tfl/programs/t_rmp_ex_dur_dose.sas-t_10080_ad_exp_dur_dose.txt

## Exposure to tralokinumab in ongoing clinical trials in AD

Exposure in ongoing trials is presented in Table 13.

**Table 13 Exposure to IMP in ongoing clinical trials in AD as of 31-Oct-2024**

| Trial | Number of subjects exposed to IMP |
|---|---|
| TRAPEDS 1 | 28 |
| TRAPEDS 2 | 6 |
| ADHAND | 198 |
| **Total** | **232** |

For TRAPEDS 2 and ADHAND, subjects are randomised 2:1 but all who remain in trial will enter open-label after week 16.
IMP: Investigational medicinal product.
Note: TRAPEDS 1, TRAPEDS 2, and ADHAND are the only ongoing Tralokinumab trials as of31-Oct-2024 in AD patients.
18NOV2024-/leo/clinical/lp0162/rmp/rmp2024/tfl/programs/t_ad_exp_ongoing.sas-t_10090_ad_exp_ongoing.

Long-term exposure to tralokinumab (≥ 12 months) is presented in Table 14 as the cumulative exposure to tralokinumab for subjects for the entire treatment period of the parent trials + ECZTEND.

**Table 14 Long-term exposure to tralokinumab – ECZTEND**

| Exposure time | Number of subjects exposed to tralokinumab |
|---|---|
| >= 52 weeks | 1552 |
| >= 64 weeks | 1503 |
| >= 80 weeks | 1430 |
| >= 96 weeks | 1373 |
| >= 104 weeks | 1336 |
| >= 120 weeks | 1268 |
| >= 136 weeks | 1156 |
| >= 152 weeks | 1017 |
| >= 156 weeks | 983 |
| >= 172 weeks | 852 |
| >= 188 weeks | 726 |
| >= 204 weeks | 606 |
| >= 208 weeks | 577 |
| >= 224 weeks | 483 |
| >= 240 weeks | 354 |
| >= 256 weeks | 241 |
| >= 272 weeks | 172 |
| >= 288 weeks | 109 |
| >= 304 weeks | 47 |
| >= 320 weeks | 3 |

Exposure time on tralokinumab from completed parent trials (ECZTRA 1-8) plus exposure time during the ECZTEND trial (open-label tralokinumab treatment) is included. AD: Atopic Dermatitis. N: Number of subjects. # Studies included: LP0162-1325, LP0162-1326, LP0162-1334, LP0162-1339, LP0162-1341, LP0162-1342, LP0162-1343, LP0162-1346 and LP0162-1337
18NOV2024-/leo/clinical/lp0162/rmp/rmp2024/tfl/programs/t_ad_expos_cum_sum_adecz.sas-t_10100_ad_exp_sum_ad ecz.txt

# Part II: Module SIV – Populations not studied in clinical trials

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

The exclusion criteria listed below are those related to the safety of the enrolled subjects.

**Subjects with elevated levels of alanine aminotransferase or aspartate aminotransferase**

Reason for exclusion: Subjects with elevated levels of alanine aminotransferase (≥2.0 times upper limit of normal) or aspartate aminotransferase (≥2.0 times upper limit of normal), both of which are indicative of moderate-to-severe hepatic impairment, were excluded from the parent trials with tralokinumab in AD, however in ECZTEND the restriction was altered, to exclude those with "clinically significant" laboratory abnormalities during the screening period. The reason to exclude these subjects was to avoid exposing subjects with moderate-to-severe hepatic impairment to tralokinumab before the safety of tralokinumab has been established in AD subjects with normal hepatic function. As a monoclonal antibody, tralokinumab is not expected to undergo significant hepatic elimination.

Is it considered to be included as missing information: No

Rationale: There was no overall difference in the safety profile of tralokinumab between subjects with normal hepatic function and mild hepatic impairment (see M2.7.4 (56) Section 5.1.4). There is no clinical data indicating that tralokinumab would cause harm to subjects with moderate-to-severe AD and moderate or severe hepatic impairment.

**Subjects with a history of anaphylaxis following any biological therapy**

Reason for exclusion: Monoclonal antibodies may induce hypersensitivity reactions in rare cases, however, the incidence of hypersensitivity reactions differs between individual monoclonal antibodies (57). As a general precaution, subjects with a history of anaphylaxis following treatment with one biological therapy should not be exposed to other biologic therapies.

Is it considered to be included as missing information: No

Rationale: No anaphylactic reactions to tralokinumab were observed in the clinical trials in AD (see Part II SVII.1.1 – and M2.7.4 (56) Section 2.1.6.6). Systemic hypersensitivity reactions, including anaphylaxis, is not considered a safety concern.

**Subjects who are pregnant, breastfeeding, or lactating**

Reason for exclusion: Subjects who are pregnant, breastfeeding, or lactating were excluded from the trials in AD to avoid exposing unborn and new-born children to tralokinumab before the safety of tralokinumab has been established in adult patients with AD. The current label also states: “As a precautionary measure, it is preferable to avoid the use of tralokinumab during pregnancy”.

Is it considered to be included as missing information: Yes

**Subjects with clinically significant systemic infections or serious skin infections requiring parenteral antibiotics, antiviral, or antifungal medication less than 4 weeks prior to randomisation**

Reason for exclusion: As IL-13 neutralisation could potentially compromise the immune response towards systemic or skin infections, subjects with clinically significant systemic infections or serious skin infections less than 4 weeks prior to randomisation were excluded from the trials in AD to prevent exposure of subjects with latent infections to tralokinumab.

Is it considered to be included as missing information: No

Rationale: Based on non-clinical testing of tralokinumab and the lower frequency of skin infections requiring systemic treatment and of severe or serious infections with tralokinumab than with placebo in the trials in AD (see M2.7.4 (56) Section 2.1.6.1 and 2.1.6.3), systemic or serious infections are not considered a safety concern.

**Subjects with a helminth parasitic infestation less than 6 months prior to randomisation that have not been treated with, or have failed to respond to, standard of care therapy**

Reason for exclusion: It is believed that the allergic response involving IL-13 has evolved to protect the host from parasitic infestation. Therefore, neutralisation of IL-13 might theoretically cause a worsening of parasitic infestation and prevent expulsion of gastrointestinal worms (helminths). To prevent exposure of subjects with latent helminth parasitic infestation to tralokinumab, subjects with such infestations less than 6 months prior to randomisation who were not treated with, or failed to respond, standard of care therapy were excluded from the trials in AD.

Is it considered to be included as missing information: No

Rationale: Based on the clinical data (no increase in frequency of serious infections in general with tralokinumab treatment compared with placebo and no helminth parasitic infestation cases considered related to tralokinumab treatment (see M2.7.4 (56) Section 2.1.6.3)) and the fact that helminth infections are rare in countries where AD is common, helminth infection is not considered a safety concern. Furthermore, the label addresses this issue, advising that those with pre-existing helminth infections should be treated before initiating treatment with tralokinumab, and that if a patient becomes infected while receiving tralokinumab and does not respond to antihelminth treatment, then tralokinumab should be temporarily discontinued until infection resolves.

**Subjects with a history of malignancy**

Reason for exclusion: IL-13 has been suggested to have anti-proliferative properties towards certain tumour cells and to down-regulate anti-tumour immunity (58, 59). To avoid exposure of subjects with latent cancer to tralokinumab, subjects with a history of cancer, except those in full remission, were excluded from the trials in AD.

Is it considered to be included as missing information: No

Rationale: The ECZTEND study, was an open label extension study in which subjects from parent trials were exposed for up to an additional 5 years' treatment with tralokinumab given as standard dose every second week. Data from this trial was described and compared with other AD populations in the M5.3.5.3 ECZTEND – Malignancy report (see section SVII.2 (New safety concerns and reclassification with a submission of an updated RMP) for further information.) The Malignancy report concluded that there was no increased risk of malignancy with up to 5 years of treatment with tralokinumab compared to placebo, dupilumab or JAK inhibitors (60).

In addition, a comprehensive assessment of the carcinogenic potential of tralokinumab has been performed based on data from repeat-dose toxicity studies, evaluation of generalised immune suppression, and evaluation of published literature (61). The conclusion of this

evaluation is that there is no indication of an increased risk of malignancy by neutralisation of IL-13. Across the tralokinumab development programme, there has been no indication of a higher risk of malignancy with tralokinumab than with placebo (see Part SVII.3. – M2.7.4 (56) Section 2.1.6.5 and M5.3.5.3 ISS (62) other indications Section 2.1.6.5).

**Subjects with a history of attempted suicide or who are at significant risk of suicide**
Reason for exclusion: A diagnosis of AD is associated with a higher risk of depression and suicidal ideation (54). To avoid exposure of subjects at significant risk of suicide to tralokinumab before the safety of tralokinumab has been established in AD subjects not at risk of suicide, subjects at risk of suicide were excluded from the trials in AD. Subjects at risk of suicide was defined as subjects who were considered at risk of suicide by the investigator or subjects who answered "yes" to at least one question on suicidal ideation or suicidal behaviour on the Colombia-Suicide Severity Rating Scale at screening.

Is it considered to be included as missing information: No

Rationale: Across the clinical trials in AD, there was no indication of increased risk of suicide (62) with tralokinumab treatment compared with placebo (M2.7.4 (56) Section 2.1.6.10).

**Subjects with tuberculosis requiring treatment within the 12 months prior to enrolment**
Reason for exclusion: Non-clinical evidence suggests that the Th2 axis (IL-4 secretion) may be associated with tuberculosis. Therefore, tralokinumab could potentially influence the course of tuberculosis infection in subjects with tuberculosis. Subjects treated for active tuberculosis within 12 months prior to enrolment were excluded from the clinical trials in AD as they have an increased risk of becoming infected again and to avoid having confounders from concomitant medication.

Is it considered to be included as missing information: No

Rationale: Since IL-13 is not an essential cytokine for macrophage or dendritic cell function in the containment of the tuberculosis bacteria during latent tuberculosis (63, 64) and specific inhibition of IL-13 is not considered to be a risk factor for reactivation of latent tuberculosis. Subjects were not screened for latent tuberculosis prior to enrolment in the trials. Across the clinical trials in AD, a single event of 'tuberculosis' was reported in the safety follow-up period by a subject in the tralokinumab group in trial ECZTRA 3. The event was reported 161 days after the first tralokinumab dose and 63 days after the latest IMP administration, was mild and non-serious, and considered possibly related to the IMP (reported in the M5.3.5.3 ISS 120-Day Safety Update (62)). Tuberculosis is not considered a safety concern.

**Subjects with immunodeficiency disorders**

Reason for exclusion: To avoid exposing subjects with immunodeficiency disorders to tralokinumab before the safety of tralokinumab has been established in immunocompetent patients with AD.

Is it considered to be included as missing information: No

Rationale: IL-13 is a regulator of peripheral cell-mediated immunity (65). Therefore, LEO Pharma does not consider the immunosuppression resulting from neutralisation of IL-13 signalling by tralokinumab to exacerbate the immunosuppression in immunodeficient subjects. Across the clinical trials in AD, the frequency of opportunistic infections was lower with tralokinumab treatment compared with placebo (see M2.7.4 (56) Section 2.1.6.3.6). Thus, there is no indication of an increased risk of opportunistic infections with tralokinumab treatment.

**Subjects with a history of immune complex disease**

Reason for exclusion: Administration of an antibody can cause accumulation of antibody-antigen complexes and cause a type III hypersensitivity (Arthus) reaction or immune complex disease (66). Therefore, subjects with a history of immune complex disease following any biological therapy have been excluded from the clinical trials.

Is it considered to be included as missing information: No

Rationale: Relatively low amounts of tralokinumab are administered and the amount of IL-13 in the body, even in high IL-13 disease states, is very low. Therefore, type III hypersensitivity reactions are very unlikely to occur. Across the clinical trials in AD, there were no observations of immune complex disease with tralokinumab (see Part II SVII.1.1 – Immunogenicity and M2.7.4 (56) Section 2.1.6.7). Immune complex disease is not considered a safety concern.

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

The clinical development programme is mainly composed of clinical trials, the size of which are determined by power calculations to prove efficacy. Clinical trials are 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.

The ECZTEND trial included subjects with AD who participated in ECZTRA trials and lasted for up to an additional 5 years. When the duration of treatment in the parent trial is added to this exposure, some patients would have received up to 6 years treatment with tralokinumab,

and therefore, this substantially addresses possible 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 15 Table Part SIV.3 – Exposure of special populations included or not included in clinical trial development programmes**

| Type of special population | Exposure |
|---|---|
| Pregnant women | No trials with tralokinumab have been conducted in pregnant women, and pregnant women were excluded from participation in all clinical trials with tralokinumab.<br><br>As of 31-Oct-2024, a total of 43 pregnancies in female subjects treated with tralokinumab and 4 pregnancies in partners of male subjects who received tralokinumab were reported (paternal pregnancies were not required to be reported in the ECZTRA protocols and were therefore not collected systematically).<br><br>The outcome of the 43 pregnancies in trial subjects treated with tralokinumab were:<br>• 18 healthy babies*<br>• 12 elective abortions<br>• 5 spontaneous abortions<br>• 1 ongoing pregnancy<br>• 1 ectopic pregnancy and finally<br>• 6 pregnancies with unknown final outcome in subjects who were lost to follow-up.<br>* For one neonate, 2 SAEs (considered not related to IMP by investigator) were reported (C-reactive protein high level and jaundice) which resulted in prolonged hospitalization; both events resolved within 5 days and no congenital anomalies or other complications were reported. The mother received the last dose of tralokinumab 9.5 months before delivery.<br><br>In all trials with tralokinumab to date, no adverse outcomes have been reported in the babies born by female subjects exposed to tralokinumab. One adverse outcome has been reported after a paternal pregnancy; the pregnancy outcome was reported as a live baby with congenital anomalies of foot malformation and skull asymmetry, both of mild severity. The skull asymmetry was considered recovered 3 days after birth. Per paediatric visit at age 3 months, both anomalies had resolved without treatment. There have been no adverse effects findings in nonclinical male fertility |

| Type of special population | Exposure |
|---|---|
| | studies in cynomolgus monkeys and due to this, there are no restrictions on fathering a child or sperm donation in trials with tralokinumab.<br><br>2 spontaneous abortions at very early gestational age have been reported:<br>• 1 at week 1 of the pregnancy (as reported by the investigator on the Pregnancy form) in a woman aged 30-40 years treated with tralokinumab for more than 1 year in ECZTRA 3/ECZTEND.<br>• 1 at gestation-week 4 (determined by early prenatal ultrasound) in a woman aged 20-30 years treated with tralokinumab for more than 2 years in ECZTRA 3/ECZTEND.<br>There are insufficient data available to draw conclusions about the safety of using tralokinumab during pregnancy, however, LEO Pharma is conducting an observational PASS of tralokinumab use in pregnancy as an additional pharmacovigilance activity (see Part III.2 for details).<br><br>As a precautionary measure, it is preferable to avoid the use of tralokinumab during pregnancy. |
| Breastfeeding women | No cases of lactation have been reported in any clinical trial with tralokinumab. Therefore, no data are available to draw conclusions about the safety of using tralokinumab during lactation. As a precautionary measure, the label will state that a decision must be made whether to discontinue breastfeeding or to discontinue tralokinumab treatment, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. |
| Subjects with relevant comorbidities:<br><br>• Subjects with hepatic impairment.<br><br>• Subjects with renal impairment. | <u>Subjects with hepatic impairment:</u><br>Subjects with moderate-to-severe hepatic impairment were excluded based on their levels of alanine aminotransferase and aspartate aminotransferase at screening. There was no difference in the overall safety profile of tralokinumab between subjects with normal hepatic function and subjects with mild hepatic impairment. |

| Type of special population | Exposure |
|---|---|
| • Subjects with cardiovascular impairment. | Mild hepatic impairment was not found to affect the PK of tralokinumab. Limited data are available in subjects with moderate or severe hepatic impairment.<br><br>Dose adjustment is not considered needed in patients with hepatic impairment.<br><br><u>Subjects with renal impairment:</u><br>Subjects with severe renal impairment were not included in the clinical trials. Tralokinumab is an immunoglobulin with a molecular mass of approximately 147 kDa, therefore, tralokinumab is unlikely to be cleared by renal filtration and excreted in the urine.<br><br>There was no difference in the overall safety profile of tralokinumab between subjects with normal renal function (estimated glomerular filtration rate [eGFR] of at least 90 mL/min/1.73 $m^2$), mildly impaired renal function (eGFR between 60 and 89 mL/min/1.73 $m^2$), and moderately impaired renal function (eGFR between 30 and 59 mL/min/1.73 $m^2$).<br><br>Mild or moderate renal impairment was not found to affect the PK of tralokinumab. Limited data are available in subjects with severe renal impairment function (eGFR below 30 mL/min/1.73 $m^2$).<br><br>Dose adjustment is not considered needed in patients with renal impairment.<br><br><u>Subjects with cardiovascular impairment:</u><br>Subjects with cardiovascular impairment that, in the opinion of the investigator, could have affected the safety of the subject were not included in the trials. Tralokinumab is unlikely to interact with ion channels due to the large size and high target specificity. No effects on electrocardiogram activity were observed in clinical trials with tralokinumab. There is no indication of increased risk of cardiovascular events with tralokinumab treatment. |
| Population with different racial origin | Across the tralokinumab development programme in AD, there was no difference in the overall safety profile of tralokinumab between race subgroups. |

| Type of special population | Exposure |
|---|---|
| | Racial origin was not found to affect the PK of tralokinumab, however, clinical safety data with tralokinumab in subjects with other racial origins than White, Asian, and Black or African American are limited. |
| Subpopulations carrying relevant genetic polymorphisms | No screening for relevant genetic polymorphisms were performed in the clinical development program. |
| Paediatric | No clinical trials with tralokinumab have been completed in paediatric subjects below the age of 12, with AD, however, clinical trials in children 2-11 years with AD are agreed as part of the EU Pediatric Investigation Plan (current decision EMA/PE/0000183430)) and are now ongoing (TRAPEDS 1 and 2).<br><br>One clinical trial, (ECZTRA 6, see Part II, SIII) investigated the safety and efficacy of tralokinumab in adolescents with AD. Tralokinumab was shown to be well-tolerated with a safety profile similar to the safety profile observed for the adult population. This has resulted in tralokinumab being approved for use also in adolescents aged 12 years and above. |
| Elderly | Across the tralokinumab development programme in AD, there was no difference in the overall safety profile of tralokinumab between elderly subjects and adults.<br><br>Age was not found to impact the PK of tralokinumab. Limited data are available in subjects >75 years of age.<br><br>Dose adjustment is not recommended in elderly patients. |

**Conclusions on the populations not studied and other limitations of the clinical trial development programme**

| Safety concerns identified from populations not studied | |
|---|---|
| Important potential risks | None |
| Missing information | Use in pregnant and lactating women |

## Part II: Module SV – Post-authorisation experience

The International Birth Date for Adtralza® is 17-Jun-2021. The world-wide marketing experience of Adtralza® was calculated using total sales volume realised from LEO Pharma to LEO Pharma affiliates, distributors, etc. Data are only available in whole months, hence the exposure data presented are for the period of 3 years and 5 months from 01-Jun-2021 to 31-Oct-2024.

As AD is a chronic disease, the treatment with Adtralza® can continue for several years.

The following assumptions have been made:

The recommended treatment course of Adtralza® is 4 injections given by prefilled syringes or 2 injections given by prefilled pens (total of 600 mg tralokinumab) administered at week 0, followed by administration of 2 injections given by prefilled syringes or 1 Injection given by prefilled pen (total of 300 mg tralokinumab) every other week.Therefore, a patient starting on Adtralza® is administered 6 syringes or 3 pens (total of 900 mg tralokinumab) in the first month of treatment and 4 syringes or 2 pens (total of 600 mg tralokinumab) every month thereafter. At prescriber's discretion, every fourth week dosing (of 2 syringes or 1 pen, total of 300 mg of tralokinumab) may be considered for patients as maintenance after 16 weeks of treatment, however, the exposure calculation in this section is based on the expected most commonly recommended treatment course.

The number of subjects treated with Adtralza® is calculated by dividing the volume of syringes by an estimated monthly consumption rate of 3.7 syringes. This factor is based on the fact that an Adtralza® patient should consume 52 pre-filled syringes every year (in a maintenance year) assuming 2 pre-filled syringes every other week, or 4.3 syringes every month. A compliance rate of 85%, which equals a consumption rate of 3.7 syringes per patient

per month, is applied based on rates for equivalent psoriasis treatments. Prefilled pens contain double the volume of the syringes. Therefore, the consumption rate is half the rate of prefilled syringes (3.7/2 = 1.85) per month.

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

**Potential for misuse for illegal purposes**

Tralokinumab is not expected to have any potential for abuse or dependence based on the mechanism of action. The safety profile of tralokinumab does not suggest rewarding effects or abuse-related behaviours related to treatment.

No evidence of potential drug abuse or misuse has been observed in the clinical trials.

Any potential risk for misuse for illegal purposes is considered negligible, hence no risk minimisation plan is deemed necessary.

# Part II: Module SVII – Identified and potential risks

## SVII.1 Identification of safety concerns in the initial RMP submission

### SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

**Potential harm from overdose**

Tralokinumab single intravenous doses of up to 30 mg/kg, which corresponds to an approximate 2100 mg dose in a subject weighing 70 kg, were found to be well tolerated in patients with asthma.

The highest multiple dose regimen evaluated was tralokinumab 600 mg Q2W, administered subcutaneously, in patients with asthma; the steady-state mean concentration was observed at

12 weeks after dosing. The tralokinumab 600 mg Q2W dose regimen was well tolerated with no apparent dose response or clustering of events compared with placebo or the lower tralokinumab dosing regimens (150 mg and 300 mg Q2W).

In the clinical trials, investigators were instructed to report events of overdose. No tralokinumab overdose events were reported in patients with AD. In patients with asthma, 1 tralokinumab overdose was reported; the subject received 2.2 mL instead of 2 mL on the first day of dosing; no associated adverse events were reported in relation to this.

Tralokinumab is available as a pre-filled syringe (150 mg in 1.0 mL) and as a pre-filled pen, (300 mg in 2.0 mL) as a single injection. It is not possible to increase the amount to be injected from the devices. Overdosing will require additional injections.

The risk associated with a tralokinumab overdose is considered negligible. No safety concern has been identified for overdose with tralokinumab.

**Potential for medication errors**

No potential or identified risks resulting from medication errors have been identified in the completed clinical trials in patients with AD. Furthermore, no medication errors considered not adequately mitigated with the implemented “Preventative measures for the final product being marketed” described below have been identified in the post-marketing setting.

Preventive measures for mitigating medication errors in the post-marketing setting

Tralokinumab is available as a 150 mg/mL solution for injection administered subcutaneously via 2 x 1 mL (300 mg) accessorised pre-filled syringes and as a 2 mL (300mg) pre-filled pen.

The products will be supplied with instructions for use (IFU) which provides step-by-step instructions on proper use and storage of the product. The IFU provides instructions in writing and graphic description on the injection technique.

Tralokinumab is to be administered in the thigh or abdomen for self-injection. It can be administered in the upper arm if injection is given by a caregiver.

Concerning the pre-filled syringe; a potential risk of underdose (injecting only 1 pre-filled syringe instead of 2) is mitigated in the IFU as well as on the carton of the pre-filled syringe by instructing the user to repeat injection, in order to receive the full dose.

Concerning the pre-filled pen; a potential risk of overdose (injecting 2 pre-filled pens) is mitigated in the IFU of the pre-filled pen by instructing the user to inject 1 pre-filled pen for a

full dose. Further, under the header IMPORTANT INFORMATION of the IFU it is stated: You will receive your full dose with 1 injection of the Adtralza® pre-filled pen.

Finally, it is described that when using the first pre-filled pen in the box to: “remove 1 pre-filled pen from the carton” and “when using the first pre-filled pen, the carton with the remaining pre-filled pen should be put back in the fridge.” This is to stress for the patient that only 1 pre-filled pen should be used for full dose.

In the human factors (HF) validation studies conducted for the pre-filled syringe in September 2019 and for the pre-filled pen in June 2022, the intended users demonstrated that they could use both -combination products safely and effectively.

The HF validation studies did not result in any patterns of use errors or difficulties on the critical tasks by the intended users under conditions of simulated use reasonably representative of the real use environment. While safety-critical errors were observed by a small number of participants in the studies, many of these were assessed as due to study artefact or a failure to read the instructions. In most cases, the error was not repeated. None of the use errors were assessed as being caused solely by design flaws in the device or instructions.

The findings suggest that the packaging, pre-filled syringe, and pre-filled pen are well designed for the target users to be able to perform the essential tasks required to administer the medicine, even when intended users are not trained. Based on the HF validation studies it can be concluded that:

- None of the observed use errors and difficulties on the critical tasks required further mitigation by modifications to the design of the device or the labelling.

- The IFU was shown to be effective in communicating safety-critical information.

- The pre-filled syringe and the pre-filled pen were found to be safe and effective in the hands of the intended users.

**Potential for transmission of infectious agents**

Tralokinumab drug substance is manufactured in a murine NS0 (non-immunoglobulin secreting) myeloma cell line by recombinant DNA technology. No materials of human origin were or are used for any of the development or manufacturing steps.

A safety program minimises the potential for introduction of adventitious infectious agents into the manufacturing process. The agents controlled are viruses, microbial contaminants and transmissible spongiform encephalopathy:

- The viral safety programme comprises 3 complementary strategies that provide assurance that the product is free from viral contamination. The first strategy is to minimise the potential for introduction of virus into the process through contaminated raw materials, cell lines, and/or environmental exposure. This includes testing of the master and working cell banks to ensure that they are free of detectable adventitious agents, using raw materials with appropriate certification, minimising the use of animal-derived materials in the manufacturing process, and using closed manufacturing operations. The second strategy is to test at appropriate stages in the manufacturing process to ensure that in-process materials are free of detectable adventitious agents. The third strategy is to provide removal and inactivation capacity for viruses through orthogonal process steps, and to demonstrate this capability through small-scale viral clearance studies. Based on the complementary strategies of the viral safety programme, the viral risk associated with this product is negligible.
- The tralokinumab manufacturing process incorporates control measures to prevent any bioburden contamination and sterility is monitored and assured throughout the manufacturing process for drug substance and drug product.
- An assessment of transmissible spongiform encephalopathy (TSE) risk was conducted for materials of ruminant animal origin (including those raw materials that may utilise animal-derived components in their manufacturing process) used in host cell culture, cell line engineering, and cell banking of the tralokinumab production cell line. Based upon the information obtained from the suppliers, the risk of transmission of TSE from materials used in the production of tralokinumab (including manufacturing of the cell bank) is extremely low. The risk assessment follows the bovine spongiform encephalopathy (BSE) risk assessment format presented in the notice by the European Commission, Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (67).

**Potential for off-label use**

Tralokinumab has been developed for the treatment of moderate-to-severe AD in adult patients who are candidates for systemic therapy.

Tralokinumab has been approved in adolescent patients, aged 12 to 17 years, with moderate-to-severe AD who are candidates for systemic therapy; the Paediatric Investigation Plan (current decision EMA/PE/0000183430) also comprises the ongoing clinical trials in children aged 2 to 11 years.

Tralokinumab could potentially be used off-label in paediatric patients as there are limited treatment options for paediatric patients with moderate-to-severe AD. The approved label and patient information state that tralokinumab is indicated for adults and adolescent patients aged 12 years and older only. Efficacy and safety in children below the age of 12 years is yet to be established.

In addition, tralokinumab could potentially be used off-label in pregnant and lactating women with moderate-to-severe AD as there are limited treatment options for this population as well. The approved label and patient information state that limited data is available in pregnant and lactating women and use with tralokinumab should be avoided in this population.

Routine pharmacovigilance will be used to monitor adverse events after tralokinumab off-label use and will be reported to regulatory authorities, as required.

**Hypersensitivity reactions**

Monoclonal antibodies may induce hypersensitivity reactions in rare cases, however, the incidence of hypersensitivity reactions differs between individual monoclonal antibodies (57). No anaphylactic reactions to tralokinumab were observed in the completed clinical trials in AD. In the clinical trials in asthma, anaphylactic reaction has been reported very rarely following administration of tralokinumab (see M2.7.4 (56) Section 2.1.6.6). Based on this, appropriate text about systemic hypersensitivity is included in the label and patient information. The risk of systemic hypersensitivity reactions after injection of a monoclonal antibody is well-known to health professionals and no additional pharmacovigilance activities or additional risk minimisation measures are suggested; these events will be followed up by routine pharmacovigilance activities.

**Immunogenicity**

Administration of an antibody can cause accumulation of antibody-antigen complexes and cause a type III hypersensitivity (Arthus) reaction or immune complex disease (66). Overall, the immunogenicity risk for tralokinumab is deemed low, primarily because tralokinumab is a human IgG4 antibody and it is unlikely that anti-drug antibodies (ADA) would cross-react with an endogenous counterpart (see M5.3.5.3 ISI (68)).

Clinical data from the trials with tralokinumab in AD as well as supportive clinical data from other indications (asthma, ulcerative colitis, and idiopathic pulmonary fibrosis) showed that the rate of ADA was low. For the ECZTRA trials (AD pool), a similar ADA incidence was observed in subjects treated with tralokinumab (1.4%) compared with subjects treated with placebo (1.3%) during the initial 16 weeks of treatment. Furthermore, only 2/1553 tralokinumab treated subjects (0.1%) and 1/629 placebo-treated subjects (0.2%) had treatment-emergent neutralising anti-drug antibodies (nAb) during the initial 16 weeks of treatment. Thus, the ADA/nAb incidence after 16 weeks of treatment was low and similar between tralokinumab and placebo confirming the low immunogenicity of tralokinumab. (see M2.7.4 (56) Section 2.1.6.7 and M5.3.5.3 ISI (68)). Across all trial periods (including treatment periods and safety follow-up), the ADA incidence for subjects who received tralokinumab was 4.6%; 0.9% had persistent ADA and 1.0.% had neutralising antibodies (see M5.3.5.3 ISS 120-Day Safety Update Report, Section 3.1.6 (62)).

Anti-drug-antibody (ADA) responses were not associated with any impact on tralokinumab exposure, safety, or efficacy in patients receiving tralokinumab for up to 6 years (in phase 2/phase 3 atopic dermatitis studies followed by the long-term extension study ECZTEND). No immunogenicity-related adverse events such as immune-complex disease, serum sickness/serum sickness-like reactions, or anaphylaxis were observed (69). Non-clinical data also suggested that there was no indication of the route of administration having an effect on ADA formation. In addition, there were no indications that ADA formation had an impact on systemic exposure or caused toxicity in any trial (see M5.3.5.3 ISI (68)).

Based on the above, there is a low immunogenicity potential of tralokinumab, and there is no scientific evidence to support the possibility of a causal relationship between immunogenicity and tralokinumab. Adverse events will be followed up via routine pharmacovigilance activities, to monitor for events possibly related to immunogenicity. No additional pharmacovigilance activities related to immunogenicity are considered necessary for tralokinumab.

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

**Table 17 Summary of safety concerns**

| Summary of safety concerns | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | Use in pregnant and lactating women |

For the justification of inclusion of the individual safety concerns (important risk or missing information) please refer to Section SVII.3.

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

The ECZTEND study, a clinical trial PASS investigating the long-term safety of Adtralza®, served as an additional pharmacovigilance activity for the safety concerns of Malignancy, Conjunctivitis, and Long-term safety. The finalized report of ECZTEND is being submitted with this RMP update.

As part of the marketing authorization application (MAA), LEO Pharma agreed with the EMA to provide two analyses presented in the M5.3.5.3 ECZTEND PASS - Malignancy report and the M5.3.5.3 ECZTEND PASS - AD pool report. The former analyses the risk of malignancy from treatment with tralokinumab and the latter compares safety data from ECZTEND to the safety data evaluated during the initial MAA (69), (60, 70).

Based on the results from ECZTEND and the additional analyses, LEO Pharma believes that sufficient information has been provided regarding the long-term safety of tralokinumab. Therefore, LEO Pharma proposes to remove the important potential risks of Malignancy and Conjunctivitis, as well as the missing information on Long-term safety, from the list of safety concerns. Detailed justifications for these proposals are provided in Sections 1.1.1, 1.1.2, and 1.1.3.

#### 1.1.1 Malignancy

In the ECZTEND trial, 19 malignancies were reported in 1672 subjects. The most frequently reported malignancies were breast cancer (5 events) and prostate cancer (3 events), which are both common types of cancer in the general population (71). No specific patterns or trends were observed for the other types of malignancies reported.

The M5.3.5.3 ECZTEND PASS – Malignancy report, compares the risk of malignancies in AD patients treated with tralokinumab in the ECZTEND trial with the risks in an AD (placebo treated) trial population, and with populations treated with dupilumab or JAK inhibitors for moderate-to-severe AD identified in published literature.

The analysis of the data in the report did not identify an increased risk of malignancy in moderate-to-severe AD subjects treated with tralokinumab for up to 5 years compared to similar patients treated with placebo, dupilumab or JAK inhibitors. In conclusion, no safety concerns or risks related to malignancy for tralokinumab were identified.

### 1.1.2 Conjunctivitis

Conjunctivitis is a known adverse drug reaction (ADR) for Adtralza®. The ECZTEND trial aimed to further understand conjunctivitis during long-term treatment, as it is common in individuals with atopic dermatitis (AD).

In the absence of a comparator arm in ECZTEND, safety data from ECZTEND was compared to the safety data available from the AD pool evaluated during the initial MAA. This comparison is presented in the M5.3.5.3 ECZTEND PASS - AD pool report.

The incidence rate of conjunctivitis in ECZTEND was lower than in the overall AD population. This is expected because the disease severity at baseline in ECZTEND was lower, and the improvement achieved in the parent trials was sustained during long-term treatment with tralokinumab in ECZTEND. The AD pool report concluded that there was no increased risk of conjunctivitis during long-term treatment with tralokinumab, considering the safety data from ECZTEND and the known association between AD severity and conjunctivitis.

### 1.1.3 Long-term safety

Based on the safety data from ECZTEND, no new risks or safety concerns were found during long-term treatment with tralokinumab 300 mg Q2W. The M5.3.5.3 ECZTEND PASS - AD pool report compared the safety data from ECZTEND to the initial AD pool for various safety topics defined by the EMA, which include:

- Systemic hypersensitivity including events associated with immunogenicity
- Conjunctivitis over longer term
- MACE
- Malignancy
- Serious infections
- Suicidal ideation, suicide, and depression

- Arthropathy, enthesitis, or tendinopathy
- Injection site reactions
- Safety in Black or African American subjects
- Overall safety in subjects ≥65 years

The incidence rates of the safety topics in ECZTEND were similar to or lower than those observed in the AD pool. The analysis in the AD pool report concluded that no safety concerns or risks associated with tralokinumab were identified in ECZTEND for the safety topics. Therefore, long-term treatment with tralokinumab 300 mg Q2W does not appear to increase the risk of events within the defined safety areas by the EMA.

### 1.1.4 Conclusion

Based on the ECZTEND data (60, 69, 70) and in line with the GVP Module V – Risk management systems (Rev 2), Conjunctivitis and Malignancy are no longer considered important potential risks and Long-term safety no longer considered missing information. Going forward these 3 current safety concerns are considered adequately monitored by routine pharmacovigilance activities. LEO Pharma therefore proposes to remove of the safety concerns (Conjunctivitis, Malignancy and Long-term safety) from the RMP.

## 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

No important identified risks and important potential risks have been identified for tralokinumab.

### SVII.3.2. Presentation of the missing information

**Table 18 Use in pregnant and lactating women**

| Use in pregnant and lactating women | |
|---|---|
| Evidence source | Tralokinumab has not been studied in pregnant or lactating women, and no information on the excretion of tralokinumab in human milk or effects on the nursing infant is available.<br>Pregnant and lactating women were excluded from the tralokinumab clinical development programme. Women of childbearing potential were required to use a highly effective method of contraception and subjects who became pregnant during a trial were to discontinue IMP permanently.<br>There is currently insufficient clinical data available to draw conclusions about the safety of using tralokinumab during pregnancy (Table 15).<br>Animal studies have not shown any effects on male and female reproductive organs or on sperm count, motility, and morphology. |
| Population in need of further characterisation | To investigate safety of tralokinumab use in pregnant and lactating women.<br>An observational study of tralokinumab use in pregnancy is ongoing.<br>Protocol ID number NIS-Tralo-2178<br>This study is categorised as a PASS. |

## Part II: Module SVIII – Summary of the safety concerns

**Table 19 Table Part SVIII.1 – Summary of safety concerns**

| Summary of safety concerns | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | Use in pregnant and lactating women |

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

## III.1 Routine pharmacovigilance activities

LEO Pharma has an appropriate pharmacovigilance system in place to monitor drug safety in accordance with the European legislation. Main routine pharmacovigilance activities consist of adverse reaction reporting, signal detection and management, Periodic Safety Update

Report (PSUR) and weekly literature review. Details regarding routine practices for conducting pharmacovigilance are described in LEO Pharma's Pharmacovigilance System Master File (PSMF).

**Specific adverse reaction follow-up questionnaires:**
Not applicable.

**Other forms of routine pharmacovigilance activities:**
To further address the missing information 'Use in pregnant and lactating women', the safety database will be used to perform supplementary surveillance of pregnancy outcomes reported in the post-marketing setting. The supplementary surveillance of pregnancy outcomes will include the details given below.

| | |
|---|---|
| Data collection points | Baseline, EDD +1 month, EDD +3 months, and EDD +12 months. |
| Follow-up | 4 follow-up attempts at each data collection point before a patient is considered lost to follow-up.<br>Check of overdue follow-ups by Global Safety department. |
| Infants | Data collection and follow-up on all infants, not only those reporting adverse events/malformations. |
| Expert | If case(s) of malformation are received, a qualified external expert will be contracted to evaluate the case(s) including categorisation of major, minor, or other. |
| Data quality and extraction | Enhanced data quality control and data correction focusing on crucial data needed for statistical data aggregation.<br>Data extraction and aggregate analysis detailed in a statistical analysis plan. |

EDD = estimated delivery date.

## III.2 Additional pharmacovigilance activities

In total, 1 post-authorisation safety study (PASS) category 3 with tralokinumab is sponsored by LEO Pharma:

- Observational PASS of tralokinumab use in pregnancy.
  Post-authorisation safety study of tralokinumab use in pregnancy: An observational study based on electronic health care data; an additional PV activity related to the missing information 'use in pregnant and lactating women'.
  The PASS is shortly described in Table 23 and the PASS protocol is provided in Annex 3.

**Table 20 Post-authorisation safety study of tralokinumab use in pregnancy**

| **Study short name and title** |
|---|
| Observational PASS of tralokinumab use in pregnancy.<br>Post-authorisation safety study of tralokinumab use in pregnancy: An observational study based on electronic health care data. |
| **Rationale and study objectives** |
| There are no indications of reproductive toxicity of tralokinumab, but the available evidence is currently insufficient to draw conclusions about the safety of using tralokinumab during pregnancy. The study will investigate whether maternal exposure to tralokinumab during pregnancy is associated with an increased risk of major congenital malformations, preterm births, infants born small for gestational age, spontaneous abortions, or stillbirths. |
| **Study design** |
| An observational cohort study comparing the risk of adverse pregnancy outcomes in 3 groups of pregnant women diagnosed with AD: 1. Exposed to tralokinumab during pregnancy. 2. Exposed to other systemic treatments used for AD during pregnancy. 3. Unexposed to systemic treatments used for AD during pregnancy. |
| Study population |
| The study population will include women from 18 through 49 years of age diagnosed with AD who become pregnant and have a pregnancy outcome during the study period. The population will be identified in electronic healthcare databases: two in the EU; Système National des Données de Santé (SNDS) in France and the German Pharmacoepidemiological Research Database (GePaRD) as well as one in the USA; HealthCore Integrated Research Database (HIRD®). |
| **Milestones:** |
| Protocol submitted to the European Medicines Agency (EMA): within 6 months of European Commission issuance of the marketing authorisation.<br>Previous protocol endorsed by PRAC March 2022. The protocol has been updated due to changes requested by the FDA during review of the submitted protocol. Changes relate to defining the study population and outcome definitions. The updated protocol version is enclosed in Annex 3). Annual progress reports to be submitted with the PSURs (2023 through 2029).<br>Q2 2027: An interim report including feasibility assessment is planned for 3 years after tralokinumab launch and reimbursement in study countries.<br>Q2 2030: End of data collection 8 years after tralokinumab launch and reimbursement in study countries.<br>Q4 2030: Final study report: 6 months after the end of data collection. |

## III.3 Summary table of additional pharmacovigilance activities

**Table 21 Part III.1: On-going and planned additional pharmacovigilance activities**

| Study Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 3** – Required additional pharmacovigilance activities | | | | |
| Observational PASS of tralokinumab use in pregnancy.<br>Post-authorisation safety study of tralokinumab use in pregnancy: An observational study based on electronic health care data<br><br>Previous protocol endorsed by PRAC in March 2022. Updated due to changes requested by FDA during review of the submitted protocol (See Annex 3) | To investigate whether maternal exposure to tralokinumab in pregnancy is associated with an increased risk of major congenital malformations, preterm births, infants born small for gestational age, spontaneous abortions, or stillbirths. | - Use in pregnant and lactating women | Annual progress reports to be submitted with the PSURs (2023 through 2029). | Yearly |
| | | | Interim report including feasibility assessment | Q2 2027 |
| | | | End of data collection | Q2 2030 |
| | | | Final report | Q4 2030 |

# Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are proposed.

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

## Risk Minimisation Plan

Relevant information is provided in the below sections.

## V.1. Routine Risk Minimisation Measures

**Table 22 Table Part V.1 – Description of routine risk minimisation measures by safety concern**

| Safety concern | Routine risk minimisation activities |
|---|---|
| Use in pregnant and lactating women | Communicate to physicians and patients that there is a limited amount of data from the use of tralokinumab in pregnant women; therefore, as a precautionary measure, it is preferable to avoid the use of tralokinumab during pregnancy.<br>Communicate to physicians and patients that it is unknown whether tralokinumab is excreted in human milk or absorbed systemically after ingestion, so a decision must be made whether to discontinue breast-feeding or to discontinue tralokinumab therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.<br><br>Relevant text is provided in the following section of the SmPC:<br>• Section 4.6 (Fertility, pregnancy and lactation)<br><br>Relevant text is provided in the following section of the PIL:<br>• Section 2 (What you need to know before you use tralokinumab) |

## 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 23 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 lactating women | Routine risk minimisation measures:<br>Communicate to physicians and patients that there is a limited amount of data from the use of tralokinumab in pregnant women; therefore, as a precautionary measure, it is preferable to avoid the use of tralokinumab during pregnancy.<br>Communicate to physicians and patients that it is unknown whether tralokinumab is excreted in human milk or absorbed systemically after ingestion, so a decision must be made whether to discontinue breast-feeding or to discontinue tralokinumab therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.<br><br>Relevant text is provided in the following section of the SmPC:<br>• Section 4.6 (Fertility, pregnancy and lactation)<br><br>Relevant text is provided in the following section of the PIL:<br>• Section 2 (What you need to know before you use tralokinumab)<br><br>Additional risk minimisation measures:<br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>Supplementary surveillance of pregnancy outcomes reported in the post-marketing setting.<br><br>Additional pharmacovigilance activities:<br>Observational PASS of tralokinumab use in pregnancy.<br>Post-authorisation safety study of tralokinumab use in pregnancy: An observational study based on electronic health care data. |

# Part VI: Summary of the risk management plan for Adtralza® (tralokinumab)

## Summary of risk management plan for Adtralza® (tralokinumab)

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

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

This summary of the RMP for Adtralza® 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 (EPAR).

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

**I. The medicine and what it is used for**

Adtralza® is authorised for the treatment of moderate-to-severe AD in adult and adolescent patients who are candidates for systemic therapy (see SmPC for the full indication). It contains tralokinumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Adtralza®'s benefits can be found in Adtralza®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage

<https://www.ema.europa.eu/en/medicines/human/EPAR/adtralza>

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

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

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

**II.A List of important risks and missing information**

Important risks of Adtralza® 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 Adtralza®. 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 lactating women |

## II.B Summary of Missing information

| **Missing information: Use in pregnant and lactating women** | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>Communicate to physicians and patients that there is a limited amount of data from the use of tralokinumab in pregnant women; therefore, as a precautionary measure, it is preferable to avoid the use of tralokinumab during pregnancy.<br>Communicate to physicians and patients that it is unknown whether tralokinumab is excreted in human milk or absorbed systemically after ingestion, so a decision must be made whether to discontinue breast-feeding or to discontinue tralokinumab therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.<br><br>Relevant text is provided in the following section of the SmPC:<br>• Section 4.6 (Fertility, pregnancy and lactation)<br><br>Relevant text is provided in the following section of the PIL:<br>• Section 2 (What you need to know before you use tralokinumab)<br><br>Additional risk minimisation measures:<br>None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>Observational PASS of tralokinumab use in pregnancy.<br>Post-authorisation safety study of tralokinumab use in pregnancy: An observational study based on electronic health care data.<br><br>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 Adtralza®.

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

One PASS is currently ongoing (Previous protocol endorsed by PRAC, Protocol ID number NIS-Tralo-2178); details are included below.

**Study short name:**

Observational PASS of tralokinumab use in pregnancy. Ongoing.

Post-authorisation safety study of tralokinumab use in pregnancy: An observational study based on electronic health care data.

Purpose of the study:

No experimental data indicate reproductive toxicity of tralokinumab, but the available evidence is currently insufficient to draw conclusions about the safety of using tralokinumab during pregnancy. The study will investigate whether maternal exposure to tralokinumab during pregnancy is associated with an increased risk of major congenital malformations, preterm births, infants born small for gestational age, spontaneous abortion, or stillbirths.

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# PART VII: Annexes

| Annex no. | Annex title | Status |
|---|---|---|
| **Annex 1** | EudraVigilance Interface | Suspended according to the 'Message to QPPV's – EURMP Annex 1 suspension' information received per e-mail 04-Dec-2020; EMA/660260/2020. |

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|---|---|---|
| **Annex 2** | Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme | Not produced as no information to report. |
| **Annex 3** | Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan | Enclosed. |
| **Annex 4** | Specific adverse drug reaction follow-up forms | Not produced as no information to report. |
| **Annex 5** | Protocols for proposed and ongoing studies in RMP Part IV | Not produced as no information to report. |
| **Annex 6** | Details of proposed additional risk minimisation activities (if applicable) | Not produced as no information to report. |
| **Annex 7** | Other supporting data (including referenced material) | Not produced as no information to report. |
| **Annex 8** | Summary of changes to the risk management plan over time | Enclosed. |