EU Risk Management Plan for Ilumetri 100 mg and 200 mg solution for injection in pre-filled syringe and Ilumetri 100mg and 200 mg solution for injection in pre-filled pen

RMP version to be assessed as part of this application:

RMP Version number:	1.6
Data lock point for this RMP:	02 Jan 2024
Date of final sign off:	02 Jun 2024
Rationale for submitting an updated RMP:	This updated RMP is submitted in the context of a variation application to add a new presentation of Ilumetri®: 200 mg solution for injection in pre-filled pen. The information for the approved RMP V 1.4 and the previous draft RMP V 1.5 was compiled in this RMP.
Summary of significant changes in this RMP:	The Part 1 Product overview has been updated in order to include the information for the new pharmaceutical form and strength: 200 mg solution for injection in pre-filled pen. Additionally, the clinical trial exposure was updated.
Other RMP versions under evaluation:	Not applicable.
Details of the currently approved RMP:	
Version number:	1.4
Approved with procedure:	EMEA/H/C/004514/II/0054
Date of approval (opinion date):	16/May/2024

QPPV name:

Cristiana Delia Canulescu

QPPV oversight declaration:

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

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Part I: Product(s) Overview

Table 1. Part I: Product Overview

Active substance(s) (INN or common name)	Tildrakizumab
Pharmacotherapeutic group(s) (ATC Code)	L04AC17
Marketing Authorisation <Holder> <Applicant>	Almirall S.A
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Ilumetri 100 mg solution for injection in pre-filled syringe Ilumetri 200 mg solution for injection in pre-filled syringe Ilumetri 100 mg solution for injection in pre-filled pen Ilumetri 200 mg solution for injection in pre-filled pen
Marketing authorisation procedure	Centralised Procedure
Brief description of the product	Chemical class: Humanized interleukin-23 antagonist
	Summary of mode of action: High affinity (297 pM), humanized immunoglobulin G1/kappa (IgG1/κ) antibody that specifically binds to the IL-23p19 subunit and blocks the interaction of human IL-23 with the IL-23 receptor. In this way, tildrakizumab inhibits the biological activity of IL-23
	Important information about its composition: Tildrakizumab is expressed as a secreted product from a suspension of Chinese-hamster ovary (CHO) cell line. Tildrakizumab is composed of two identical heavy chains of 446 amino acids each and two identical light chains of 214 amino acids each linked by interchain disulfide bonds
Hyperlink to the Product Information	13-pi
Indication(s) in the EEA	Treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy
Dosage in the EEA	The recommended dose of Ilumetri is 100 mg by subcutaneous injection at weeks 0, and 4 and every 12 weeks thereafter. In patients with certain characteristics (e.g. high disease burden, body weight ≥ 90 kg) 200 mg may provide greater efficacy.
Pharmaceutical form(s) and strengths	Solution for injection in a single use pre-filled syringe. Each pre-filled syringe contains 100 mg tildrakizumab in 1 ml Solution for injection in a single use pre-filled syringe. Each pre-filled syringe contains 200 mg tildrakizumab in 2 ml Solution for injection in pre-filled pen. Each pre-filled pen contains 100 mg of tildrakizumab in 1 mL Solution for injection in pre-filled pen. Each pre-filled pen contains 200 mg of tildrakizumab in 2 mL.
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(s) and target population(s)

Indication

Tildrakizumab is indicated for "the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy".

SI.1 - Epidemiology of the disease

Plaque type psoriasis is of great importance in dermatology as it produces significant morbidity, has a high impact on patient health-related quality of life (HRQoL), and is of great socioeconomic importance for health care systems (Augustin, 2008). It may be associated with painful, debilitating and highly visible symptoms, affecting everyday work and social activity as well as personal and sexual relationships (Dubertret, 2006). Depending on its severity, the disease can lead to a substantial burden in terms of psychosocial stigmatization (Pathirana, 2009).

- Incidence and prevalence

Incidence

Overall, approximately 2-3% of people are affected by this disease worldwide. Three studies have reported the incidence of psoriasis in adults - two from the United States and one from Italy. The two estimates in the United States were similar (78.9/100,000 person-years (95% CI: 75.0–82.9) and 82/100,000 person-years (95% CI: 77–89), the last one being confined to women. (Icen, 2009) found a higher incidence of psoriasis in men than in women (85.5/100,000 person-years vs 73.2/100,000 person-years). Combining the two studies from the United States, which both used the Rochester Epidemiology Project database, it appeared that whereas the incidence was higher in girls than in boys until 18 years of age, thereafter psoriasis affected men more frequently than women. In the same study, data showed an increasing trend in the incidence of psoriasis in adults over a 30-year period. The Italian study reported a much higher incidence rate of 230/100,000 person-years in 2005 (Parisi, 2013). In 2012, a 2-week psoriasis screening study via medical consultation was performed in three countries simultaneously; Algeria, Tunisia and Morocco, where the incidence of psoriasis was estimated at 1036/100,000, 1326/100,000 and 1504/100,000 person-years, respectively (Ammar-Khodja, 2015).

Prevalence

Published data on the worldwide prevalence of psoriasis in countries vary between 0.09% in the United Republic of Tanzania (Gibbs, 1996) and 11.4% in Norway (Danielsen, 2013). There is also evidence to suggest that the prevalence of psoriasis may be increasing (Danielsen, 2013). In most developed countries, the prevalence is between 1.5 and 5% (Parisi, 2013).

According to European Federation of Pharmaceutical Industries & Associations (EFPIA), in Europe, it is estimated that plaque psoriasis has a prevalence of about 0.8%, i.e., the disease affects about 3.7 million Europeans, with about 2.4 million people considered to have moderate to severe disease. Psoriasis usually occurs in young adults (15-40 years, with mean age of onset of 33), with men and women equally likely to be affected. Amongst the Western industrialized countries, there is a prevalence of 1.5 – 2% (Kolios, 2016).

According to the Thomson Reuter's Incidence and Prevalence Database, which provides prevalence rates of psoriasis for countries within the EU, variability amongst the countries is seen. The lowest prevalence rate of 0.4% was seen in Portugal and the highest prevalence rate in adults of 5.2% was documented in France (the 15+ age category had a lower prevalence rate of 2.4%). Amongst the other EU countries, the following prevalence rates were documented; Belgium was 2% (15+ age category), Denmark was 3.7% (adults), Germany was 1.4 % (15+) and 2% (16 to 70 years), Italy was 1% (15+) and 3.1% (adults), Norway was 1.4% (unspecified ages), Spain was 1.8% (15+) and UK was 0.9% (unspecified ages) and 2.2% (adults).

More specific country information for plaque psoriasis exists for Norway which estimates a prevalence of moderate to severe plaque psoriasis of 0.14% (Polyzoi, 2016). In Italy, the estimated population prevalence is 2 – 3 % (Mantarro, 2013).

Psoriasis appears to occur most commonly in populations of northern Europe (Danielsen, 2013, Bo, 2008) and least in populations of eastern Asia (Shao, 1987; Chen, 2008; Yang, 2007; Li, 2012; Chang, 2009; Yip, 1984; Ding, 2012; Wang, 2012; Koo, 2017; Kubota, 2015). Some studies investigated the ethnic differences in the prevalence of psoriasis. According to a 2001 study in the United States, people with Caucasian or Black ancestry and others had a prevalence of 2.5%, 1.3% and 1.0%, respectively (Stern, 2004). In another United States study from 2009–2010, these differences were higher, with the prevalence for Caucasians, Blacks, Hispanics and others at 3.6%, 1.9%, 1.6% and 1.4%, respectively (Rachakonda, 2014).

- Demographics of the target population – age, sex, race/ethnic origin.

Studies reporting age-specific incidence rates showed a dual peak of psoriasis around 30–39 years of age and a second peak around 50–59 or 60–69 years of age. It is believed that the bimodal distribution of psoriasis incidence represents two clinical presentations of the disease, type I (early-onset) and type II (late-onset), which are defined as presenting at ≤40 and >40 years of age, respectively (Parisi, 2013).

According to Parisi et al. (2013), there was no agreement about whether the prevalence of psoriasis differed between men and women. No differences in the frequency of psoriasis between genders were found in Taiwanese children, in the United States and Norway in adults, and in the United States, United Kingdom, Norway, Spain, Scotland and Taiwan in individuals of all ages combined. Other studies reported a slightly higher prevalence of psoriasis in female subjects than male subjects in Swedish children (0.5% vs 0.1%) and in Germany (0.76% vs 0.66%); in the United States (2.5% vs 1.9% with an odds ratio=1.37 (95% CI: 1.14–1.64)) and in Norway (1.6% vs 1.2% (Lapps) and 1.4% vs 0.9% (non-Lapps)) in adults and in all ages, respectively. In contrast, psoriasis was more frequent in men than in women in Denmark (4.2% vs 3.3%, not significant) and in Australia, where it was reported to be almost twice as high in men as in women (8.9% vs 4.5%), and in individuals of all ages in Sweden (2.3% vs 1.5%) and China (0.17% vs 0.12%). Higher prevalence rates have been reported at higher latitudes, and in Caucasians compared with other ethnic groups (Parisi, 2013).

- Risk factors for the disease

Genetic factors

A multicenter meta-analysis including data from 9,389 psoriasis patients and 9,477 control subjects was performed to investigate the contribution of the deletion of genes *LCE3C* and *LCE3B*, involved in skin barrier defence, to psoriasis susceptibility in different populations. The study confirms that

the deletion of *LCE3C* and *LCE3B* is a common genetic factor for susceptibility to psoriasis in European populations [OR Overall = 1.21 (1.15–1.27)], and for the first time directly demonstrated the deletion's association with psoriasis in [Chinese OR = 1.27 (1.16–1.34); Mongolian OR = 2.08 (1.44–2.99)] populations (Riveira-Muñoz, 2011).

In previous studies, several loci have been identified as psoriasis risk susceptibility factors, with *PSORS1*, a Major Histocompatibility Complex (MHC) class I region on chromosome 6p21, being the locus with the largest effect identified to date. Within *PSORS1*, the *HLA-Cw06* allele has been pinpointed as the risk variant that confers the strongest susceptibility to psoriasis. The analysis of the *HLA-Cw6* locus showed significant differences in the epistatic interaction with the *LCE3C* and *LCE3B* deletion in at least some European populations, indicating epistatic effects between these two major genetic contributors to psoriasis (Riveira-Muñoz, 2011).

Environmental factors

Psoriatic activity in a susceptible individual can be provoked by non-specific triggers such as mild trauma (scratching, piercings, and tattoos), sunburn, or chemical irritants. Systemic drugs such as β blockers, lithium, antimalarials, and non-steroidal anti-inflammatory agents can exacerbate the disease. Psoriasis can be triggered or substantially aggravated by occupational risk factors impairing the skin barrier function. In such cases, in particular with palmoplantar psoriasis, the patient's work environment should be assessed, and adequate protective measures put in place. HIV infection might also be a trigger of psoriasis because the prevalence of psoriasis in HIV-infected patients is the same or slightly higher than in the general population, and HIV-infected patients with pre-existing psoriasis often have a flare of lesions that are difficult to treat (Boehncke, 2015).

Immunologic factors

Involvement of the immune system in psoriasis is now widely accepted. Psoriatic skin lesions originate as a result of dysregulated interactions of innate and adaptive components of the immune system with resident cutaneous cell types. The central mechanisms by which this disease develops are: the cross-talk between innate and adaptive immunity and the central role of TNFα; the interleukin 23/T helper cell 17 (Th17) axis; and the effect of immune reactions on other cells in the skin. TNFα is a pro-inflammatory cytokine that amplifies inflammation through several distinct pathways. It is produced by a broad range of cells including macrophages, lymphocytes, keratinocytes and endothelial cells, enhancing the induction of secondary mediator factors and adhesion molecules all of which have been implicated in the onset and development of psoriasis (Boehncke, 2015).

Interest is rising in the interleukin 23/Th17 axis and has resulted in several novel targeted therapies. Th17 cells are a subset of T-lymphocytes that express interleukin 17A (IL-17A) which plays a predominant role in the pathogenesis of psoriasis and other inflammatory disorders (Boehncke, 2015). The IL-17A pro-inflammatory cytokine is the primary effector of Th17 cells (Langley, 2014). It is mainly produced by Th17 cells, which derive from naïve CD4 (+) cells after stimulation by the transforming growth factor beta (TGF- beta) and interleukin 6 (IL-6) (Hollins, 2006). It is also produced by other type of cells in psoriatic lesions, including gamma –delta T cells, neutrophils and possibly mast cells. IL-17A stimulates keratinocytes to secrete chemokines and other pro-inflammatory mediators that recruit additional inflammatory cells including neutrophils Th17 cells, dendritic cells and innate lymphoid cells. Therefore IL-17A potentially acts as a master cytokine in the pathogenesis of psoriasis. Additionally, it has been shown that this cytokine plays a crucial role in the pathogenesis of several other immune-mediated diseases, including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and multiple sclerosis (Langley, 2014).

Based on this understanding, new treatments, such as Monoclonal antibodies (mAbs) and new small molecules focused on blocking the principal targets of this immunologic pathogenesis of the disease have been developed and approved in Europe and US.

- Main treatment options

A variety of systemic medications are used for the treatment of moderate to severe plaque psoriasis, particularly for patients with more than 10 percent body surface area involvement. Options for systemic therapies include immunosuppressive or immunomodulatory drugs. These therapies can be divided into 3 types: conventional systemic therapy, which includes fumaric acid esters (FAEs), methotrexate, cyclosporine and acitretin; biological therapies, which include TNFα inhibitors monoclonal antibodies (MABs) such as interleukin (IL) inhibitors; and newly developed small molecule systemic therapy such as the phosphodiesterase 4 (PDE4) inhibitor apremilast (EMA/PRAC/613102/2015).

Conventional systemic therapy

- Methotrexate*:* Over the past four decades, methotrexate has been used extensively for the treatment of psoriasis, despite the lack of rigorous clinical data supporting its use in this regard.
  A systematic review of the literature found no well-designed randomized controlled trials of methotrexate for psoriasis. Based on available clinical data, primarily derived from retrospective studies, case studies and case reports, the authors suggested that methotrexate may reduce the severity of psoriasis. (Naldi, 2005).
- Ciclosporin*:* The efficacy of ciclosporin in the treatment of psoriasis has been established in clinical trials. A systematic review of the literature identified 18 randomized clinical trials of ciclosporin therapy for psoriasis. However, despite numerous studies, none included large sample sizes, which results in an imprecise treatment effect estimate. The size of the treatment effect is quite variable between the trials, with the mean rate difference in studies of ciclosporin induction therapy ranging from slightly greater than zero to more than 0.8; the highest value occurred in a trial that required only a 50% improvement in Psoriasis Area and Severity Index (PASI) (PASI-50 response) as a measure of treatment success (Naldi, 2005).
- Acitretin: Very few studies have evaluated the short-term efficacy of acitretin in plaque psoriasis. A study that examined efficacy at 8 weeks in patients who received an initial dose of 10, 25, or 50 mg of acitretin reported a mean reduction in PASI of 61%, 79%, and 86%, respectively, in the 3 treatment groups as compared to 30% in the placebo group. The available studies on the efficacy of the drug have very varied designs and objectives. Overall, initial doses of between 40 and 50 mg/d have achieved a 50% reduction in PASI (PASI 50) in 66% to 85% of patients and a 75% reduction (PASI 75) in 34% to 52% of patients at 8 to 12 weeks. Higher dose regimens up to 70 mg/d were associated with adverse effects that make it difficult for patients to continue treatment. Clinical experience has shown acitretin to be a choice for long-term maintenance therapy because the clinical response is sustained and there is no significant loss of efficacy over time (Carretero, 2013).

Biological therapy

In the past decade, several biologics therapies have been developed and approved for the treatment of psoriasis. With the exception of etanercept, which is a fusion protein, the approved biologics are

monoclonal antibodies (MABs). TNFα inhibitors etanercept, adalimumab, and infliximab are approved for the treatment of psoriasis and psoriatic arthritis, and golimumab has been approved for psoriatic arthritis. Secukinumab interferes with the development of Th17 lymphocytes, which are important effector cells in psoriatic inflammation. Ustekinumab, a drug that blocks interleukin 12 and 23, is also approved for both indications.

TNFα inhibitors are generally used after phototherapy and when conventional systemic therapies have either failed, were not tolerated, or were contraindicated. This second-line use is in part because of the high direct costs for drugs, which are in the order of ten-times higher than for conventional systemic drugs (Boehncke, 2015).

- Secukinumab was approved as the first biological blocking IL-17A, a key effector cytokine produced by TH17 and other cells. Secukinumab is a MAB that selectively binds and neutralizes interleukin 17A (Langley, 2014) and by so doing reduces the symptoms of psoriasis. It has been compared with placebo in four main clinical trials involving 2,403 patients with psoriasis, some of whom had had previous systemic treatment for the condition. These studies showed that secukinumab is effective in improving symptoms of psoriasis, and it was thus approved to treat moderate to severe plaque psoriasis in adults who require systemic treatment (EPAR Cosentyx, 2015).
- Ustekinumab is a human MAB that that blocks the human cytokines interleukin (IL-) 12 and IL-23. Ustekinumab has been demonstrated to be effective in the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate or PUVA (EPAR Stelara, 2014).
- Recently, in April 2016 a new MAB, ixekizumab (Taltz), has been approved by the EMA and the FDA. Taltz is available as an 80 mg solution for injection. Ixekizumab is a MAB that binds with high affinity and specificity to both forms of interleukin 17A (IL-17A and IL-17A/F). Neutralisation of IL-17A by ixekizumab inhibits keratinocyte proliferation and activation which have been implicated in the pathogenesis of psoriasis. Taltz has demonstrated to be effective in the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy (EPAR Taltz, 2016).

Small molecules

Research over the past decade in inflammatory diseases such as psoriasis has focused upon the modulation of cyclic monophosphate (cAMP) a naturally occurring intracellular secondary messenger that maintains immune homeostasis by modulating pro-inflammatory and anti-inflammatory cytokines. PDE4 is cAMP-specific phosphodiesterase (PDE) and the dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP, which in turn down-regulates the inflammatory response. Apremilast is a small molecule that specifically inhibits PDE4 thereby elevating intracellular cAMP levels and controlling inflammatory response in several conditions such as psoriasis (Strand, 2013). Apremilast has been investigated in two main clinical trials involving a total of 1,257 patients with moderate to severe psoriasis plaques in which it was compared with placebo (EPAR Otezla, 2015). The benefit of apremilast is only moderate but the advantage of the oral route and the low incidence of adverse reactions makes it useful in some patients.

- Mortality and morbidity (natural history)

Psoriasis can significantly influence a person's quality of life. One study suggests that the physical and mental disability experienced with this disease was comparable or in excess of that found in patients with other chronic illnesses such as cancer, arthritis, hypertension, heart disease, diabetes, and depression (Kurd, 2010).

Although psoriasis is usually not *per se* life threatening, it is a lifelong illness with remissions and exacerbations and is sometimes refractory to treatment. It progresses to arthritis in about 10% of cases and about 17-55% of patients experience remissions of varying lengths (Kurd, 2010).

Mild psoriasis does not appear to increase risk of death**.** However, men with severe psoriasis died 3.5 years earlier compared with men without the disease. Women with severe psoriasis died 4.4 years earlier compared with women without the disease (Gelfand, 2006).

SI.2 - Concomitant medication(s) in the target population

Topical therapy is used in mild to moderate plaque psoriasis; therefore, some of these medications could be concomitantly used in the target population. Topical therapy includes topical corticosteroids, vitamin D analogues, tazarotene, tacrolimus, pimecrolimus, emollients, salicylic acid, anthralin, and coal tar (Menter, 2009).

Patients with psoriatic arthritis usually receive systemic therapy such as non-steroidal anti-inflammatory drugs with or without intra-articular infiltration with glucocorticoid. Moderate to severe forms of psoriatic arthritis are usually treated with disease-modifying antirheumatic drugs (DMARD) such as methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide. Less frequently used medications include gold salts, azathioprine, and cyclosporine. For refractory cases anti-TNFα agents (adalimumab, etanercept and infliximab) are used (Oliveira, 2015).

Common comorbidities associated with psoriasis included psoriatic arthritis, hyperlipidaemia, hypertension, diabetes, obesity, coronary heart disease, cerebrovascular disease, peripheral vascular disease, depression, anxiety, rheumatoid arthritis, Crohn's disease or ulcerative colitis, multiple sclerosis, skin cancer, lymphoma, other autoimmune disorders, and other malignancies (Feldman, 2015). Other medications used for the treatment of the other comorbidities associated with psoriasis include: antidepressants, antidiabetics and cardiovascular/antihypertensive agents and nonsteroidal anti-inflammatory (Feldman, 2015).

In a recent assessment of 1203 in-patients hospitalized for severe psoriasis and receiving medications for co-morbid disease the percentages of patients on various co-medications was as follows; ACE inhibitors 12.3%, oral anticoagulants 11.3%, diuretics 12.4%, thyroid drugs 9.9%, beta blockers 7.9%, psycholeptics 5.6%, NSAIDS 7.0%, lithium salts 0.7% and interferon alpha 0.25% (Zahl, 2005).

SI.3 - Important co-morbidities found in the target population.

Psoriasis affects multiple systems in addition to the skin. Because of the immune dysregulation and ensuing inflammation, psoriasis is associated with an increased risk of various comorbidities. Psoriatic arthritis is a common comorbidity affecting 6%-42% of psoriasis patients. Psoriatic arthritis has clinical presentations of pain and swelling of the joints, which can progress to joint damage and long-term disability.

Psoriasis is also associated with a higher prevalence of metabolic syndrome (e.g., obesity, hypertension, hyperlipidaemia, and diabetes); cardiovascular diseases (e.g., myocardial infarction

and stroke); other autoimmune diseases (e.g., inflammatory bowel diseases such as Crohn's disease and ulcerative colitis); and non-melanoma skin cancer and lymphoma. Because patients often feel stigmatized, they may develop mental health conditions, such as depressive symptoms and psychiatric disorders. The burden of comorbidities increases with disease severity among psoriasis patients (Feldman, 2015; Gulliver,2008; Vlachos, 2016).

In psoriatic patients with a history of at least one hospital admission due to psoriasis, there is about a 50% increase in cardiovascular death as compared with the general population [standardized mortality ratio (SMR) = 1.52]. In those patients with 3 or more hospital admissions, the SMR increased to 1.82. There appears to be a relationship with disease severity (Mallbris, 2004).

In a population-based cross-sectional study in the UK, the risk of metabolic syndrome (MS) increased with disease severity. In addition, the associations with the metabolic syndrome components, obesity, hypertriglyceridemia and hyperglycemia increased with the severity of psoriasis, independently of other components of MS (Langan, 2012).

A systematic review of 90 studies confirmed that patients with psoriasis had a higher risk of ischemic heart disease, stroke, cardiovascular disease and peripheral arterial disease compared with controls (Patel, 2011). Another study identified psoriasis as an independent risk factor for cardiovascular disease in women, especially if they had psoriatic arthritis and suffered from psoriasis for a longer time period (>9 years) (Li, 2012).

Severe psoriasis was associated with a greatly increased risk of chronic kidney disease (CKD) in a recent study of more than 800,000 patients, including 142,883 with psoriasis, 7,354 with severe psoriasis, and 689,702 without psoriasis. After adjustment for age, sex, cardiovascular disease, diabetes mellitus, hyperlipidaemia, hypertension, use of nonsteroidal anti-inflammatory drugs, and body mass index, the adjusted hazard ratio for CKD among patients with severe psoriasis was 1.93. In a nested analysis of 8,731 psoriasis patients and 87,310 controls, the odds ratio of CKD after adjustment for demographical factors, cardiovascular risk, use of nonsteroidal anti-inflammatory drugs, and duration of observation was 1.36 in patients with moderate psoriasis and 1.58 in those with severe psoriasis. The relative risk for CKD was highest in younger patients (Wan, 2013).

Patients with psoriasis have an increased prevalence of the psychiatric disorders anxiety and depressive disorders (30% and 60% respectively). About 10% of psoriasis patients consider the possibility of suicide (Gupta, 1998). Patients with psoriasis are at a higher risk of depression, suicidal ideation, suicide attempt and completed suicide (Gupta, 1998; Kurd, 2010; Koo, 2017).

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

A comprehensive safety evaluation of MK-3222 (tildrakizumab) was performed according to ICH S9 (R2) requirements using relevant species, the cynomolgus monkey for MK-3222 studies, and with a murine analogue in mice.

The following studies were not warranted for MK-3222 per International Conference on Harmonization (ICH) guidelines: safety pharmacology studies (ICH S6 (R1) and ICH S7A); carcinogenicity studies (ICH S9); genotoxicity studies ICH S6 (R1); and phototoxicity studies (ICH S9 and ICH S10).

Overall, there were no non-clinical findings of concern to human use:

Pharmacology

Pharmacology studies support the MoA via binding to the IL-23p19 subunit which, unlike IL-12/23p40, is not shared with IL-12. MK-3222 does not bind to IL-12. Comparison of the human and non-human primate amino acid sequence of the mature IL-23p19 subunit shows that there is between 98 to 100% identity. The use of the cynomolgus monkey as a model is supported by *in vitro* binding affinities measured by Surface Plasmon Resonance that yielded K_D of 297 pM to human, and 47 pM to cynomolgus IL-23, while no binding was observed to rat or mouse IL-23 (Report PD001 – MK-3222 (SN 08197)).

Safety pharmacology

Safety pharmacology observations were included in 3- and 9-months repeat dose toxicity studies in the cynomolgus monkey (Reports SN 07184 and SN 07329). No ECG changes were reported. From the 9 months study where detailed analysis of blood pressure, respiratory rate, and clinical observations including behaviour were provided there were no test article related findings.

Pharmacokinetics (ADME)

Pharmacokinetic profiling in the cynomolgus monkey demonstrated that MK-3222 by the IV route had biphasic serum concentration-time profiles with initial drug distribution during the first several days followed by a slow decline (t½ = 22.8 days), low clearance and limited extravascular distribution. Following single dose SC administration, MK-3222 was absorbed slowly with a mean time of maximal plasma concentration (T_{max}) of 3.00 to 4.67 days, was eliminated slowly (mean t½ values ranging from 10.0 to 21.3 days) and systemic exposure increased with increasing SC dose from 0.4 to 40 mg/kg (Module 5.3.3.1: P05776).

No indirect effects on P450 enzymes via cytokines were detected and it was concluded that drug-drug interactions through P450 pathways are unlikely.

There was negligible milk secretion of the product. MK-3222 was shown to distribute across the placental barrier. After repeated dosing to pregnant cynomolgus monkeys, serum concentrations were quantifiable in the foetus, but the reproduction toxicity studies (see below) did not reveal any untoward effects.

Toxicology

Studies included single and repeated dose toxicity, reproductive and developmental toxicity in Cynomolgus monkeys, and local tolerance in the rabbit. Additional toxicity assessments such as antigenicity and immunotoxicity were also performed, where some mechanistic studies were

performed in mice using a murine anti-IL-23 mAb in mice to detect off-target effects on host defence and immune surveillance.

MK-3222 was well tolerated in the toxicology studies with the NOAEL being the highest dose tested in all nonclinical safety studies except for the peri- and post-natal development study (PPND), where a NOAEL of 10 mg/kg/day was encountered.

No toxicological findings (including assessment of reproductive organs, hormonal effects or cardiovascular, respiratory, or CNS function) were seen in cynomolgus monkeys chronically treated with MK-3222 SC injections of 100 mg/kg every 2 weeks for 9 months. In particular, assessment for the potential for effects on male and female fertility was evaluated by examination of reproductive tract (organ weights and histomorphologic evaluation) within the repeated dose toxicity studies using sexually mature monkeys in accordance with ICH S6(R1) Preclinical Safety Evaluation for Biotechnology-Derived Pharmaceuticals. Both the 3- and 9-month studies included sexual mature animals as determined by morphological examination of the testes and/or testicular weight in males and vaginal swabs, evidence of menses, and/or hormone measurements (estradiol and progesterone) in females. No MK-3222-related effects were detected. In addition, the potential impact of IL-23 neutralization on fertility and reproductive potential was examined in mice genetically deficient in IL-23p19 (IL-23p19-/-) or IL-23 receptor (IL-23R-/-). The breeding records revealed no apparent reproductive issues for these strains as reflected by litter size and distribution of the sexes for either strain (Module. 2.6.3.1, Report PD011 – MK-3222 (SN 08220)).

In the Embryo-Foetal development (EFD), no malformations or embryo-foetal toxicity were observed in foetuses from pregnant monkeys administered MK-3222 up to 300 mg/kg SC every 2 weeks from gestation days 20 to 118.

In a PPND study, no MK-3222-related increase in pregnancy loss or infant loss rates were observed, and no effects on morphological or immunological development were observed in offspring from pregnant monkeys administered MK-3222 up to 100 mg/kg SC every 2 weeks from GD50 until parturition. With the exception of two icteric neonatal deaths from monkeys at 100 mg/kg, the other neonatal losses (one in the placebo group, two in the 10 mg/kg group and two in the 100 mg/kg group) were clearly related to maternal neglect, which is a common background finding in primagravid monkeys and not related to the treatment with MK-3222. Systemic exposure multiples calculated using the mean clinical exposure ($AUC_{0-\infty}$ of 1130-1280 µg·day/mL) from Phase 1 studies at 200 mg (P05576 and P06306) and corrected for dosing interval differences yielded a margin of 9 based on the PPND (and >80 or higher in all other pivotal studies).

Histological findings in the two icteric neonates at 100 mg/kg included lymphoid depletion in thymus (both animals) and depletion of lymphoid follicles in the spleen (one animal), and changes in the liver and kidneys were suggestive of a viral infection. While the lymphoid organ findings are consistent with stress, the cause of findings in the liver and kidney potentially related to a viral infection is unclear based on the lack of histological control data from these studies. Early perinatal and neonatal mortality (BD 1-30) caused by infections, such as sepsis, enteritis and meningitis, have been observed in untreated nonhuman primates (Module 2.4.4.5.3).

The potential relationship between the treatment with MK-3222 and increased viral infection is not supported by the mechanism of action of MK-3222. Activity of MK-3222 is based on the selective inhibition of Th17-mediated inflammatory pathway via IL-23p19 subunit that counteracts inflammation-induced tissue damage by blocking the key inflammatory cytokine (IL-12, IFNγ, IL-17, IL-6, IL-8, GROα, TNFα) response with a minimal (if any) effect on Th1-mediated immunity via IL-12 and IFNγ. Of all these cytokines, IL-12 and IFNγ are primarily involved in host defence against infections, including viral infections. This selective mechanism of action is supported by all available data indicating that MK-3222 is not associated with an increased infection risk. These considerations include the following (Module 2.4.4.5.3):

1) results of host defence studies in mice using murine anti-IL-23p19 surrogate antibody or IL-23p19 null mice;

2) toxicology studies with MK-3222 in monkeys;

3) immunotoxicology evaluation of 6 months old monkey infants exposed to MK-3222 in utero;

4) literature related to immunity against infections during pregnancy; and

5) results from a large human study (N = 200 patients) (Module 2.7.4.2) shows a protective effect of the functional IL-23R R38IQ on recurrent spontaneous abortion.

To conclude: While these findings cannot be discounted for lack of background data, the weight of evidence does not indicate a detrimental effect of MK-3222 on immune function, and the neonatal deaths are therefore considered not relevant to human risk despite a moderate exposure multiple (i.e., ≥9-fold).

Antigenicity

There was no evidence of hypersensitivity or anaphylaxis due to potential antigenicity induced by MK-3222 in the routine repeat-dose toxicity studies in monkeys. A low incidence of ADA was noted in the nonclinical safety program which did not impact the toxicity profile of tildrakizumab.

Immunotoxicity

IL-23 activates components of the innate and adaptive immune system, therefore, inhibition of this pathway by MK-3222 would be predicted to contribute to host defence and was investigated using various infection models in mice. These mechanistic studies demonstrated that inhibition of the IL-23 pathway had a decreased infection liability compared to other immunomodulatory agents (i.e., anti-TNFα and anti-IL-12/23p40 mAb). Results in the repeat-dose toxicity studies in cynomolgus monkeys showed no evidence of autoimmune or inflammatory adverse effects or any adverse effects on lymphoid tissues. In these studies, the combination of hematologic, organ weight, and macroscopic and light microscopic evaluation provided a compelling weight of evidence that MK 3222 was not associated with a cause for immunotoxicity concern. Therefore, in accordance with ICH S8 (2005), no additional immunotoxicity studies were conducted.

Immune surveillance

Immune modulatory therapy may impact immune surveillance of cancers or growing, but not yet clinically detected, occult malignancies. C57Bl/6 mice transplanted with a PDV squamous carcinoma cell line were used to evaluate the effect of specific neutralization of IL-23 on immune surveillance as an indication of tumour risk. The preclinical tumour model results demonstrate that anti-IL-23 specific blockade would not be expected to incur any worse tumour risk profile in humans than the existing anti-IL-12/23p40 therapy (e.g., ustekinumab). Moreover, MK-3222 is anticipated to have a superior tumour risk profile than the anti-IL-12/23p40 class based on the results from pre-clinical models. This approach was discussed in a follow-up scientific advice with CHMP on 24th May 2012 (EMA/CHMP/SAWP/288904/2012). The CHMP agreed that no additional non-clinical studies would be required. The CHMP also commented that: performing rodent carcinogenicity studies with surrogate antibodies will not provide valuable information on human carcinogenic potential; that the human situation is more complex than the murine models used and may vary with underlying disease; while the absence of pre-neoplastic histological changes in the 9-months monkey study is encouraging, the applicant needs to provide a detailed analysis of the literature on the cancer risk in the target population that could be associated with the mechanism of action. This information is provided in the Nonclinical Overview (Module

2.4.4.4). To summarise, results from all internal and external studies indicate that the majority of the models performed using anti-IL-23p19 antibodies (similar to MK-3222) or IL-23p19 deficient mice demonstrated a benefit to the host due to reduced tumour incidence or reduced tumour growth.

In contrast, the majority of the models demonstrated that IL-12/IL-23 dual blockade resulted in impaired tumour surveillance and increased tumour burden.

The weight of evidence demonstrates a benefit due to reduced tumour incidence or reduced tumour growth following specific IL-23 blockade (i.e., MK-3222) and that specific IL-23p19 inhibition has reduced risk with respect to carcinogenic potential in comparison to broader IL-12/23p40 inhibition.

In addition, no pre-neoplastic histological changes were observed in the 9-month chronic toxicity study in cynomolgus monkeys with the clinical candidate, MK-3222, where high exposure to the drug (>100-fold above the clinical exposure in patients) was maintained over the course of the study. Moreover, the safety profile of ustekinumab (Stelara®, anti-IL-12/23p40 mAb) or MK-3222 does not suggest an increased risk for malignancies in clinical studies with either mAb.

Local tolerability

MK-3222 was well tolerated by different routes (IV; SC; as well as potential routes for misapplication [intra-arterial, intramuscular, and paravenous injection]) of administration.

Additional nonclinical data

The non-clinical pharmacology, pharmacokinetics and toxicology of MK-3222 is well characterised. There is no need for additional non-clinical data to support benefit/risk assessment.

Conclusions on non-clinical data

Non-clinical data reveal no special hazard for humans based on conventional studies of mechanism of action, primary or secondary pharmacodynamics, safety pharmacology, ADME properties, repeated dose toxicity, fertility, embryo-foetal development, and local tolerance.

Neonatal deaths possibly due to viral infection, with an unclear relationship to the test article, were observed in monkeys. Based on weight-of-evidence, there is no evidence of potential increased risk of sensitivity to viral infections in neonates, nor in adults, from non-clinical data. Therefore, these data need not be considered in Sec. 5.3 of the SmPC.

A detailed literature review of the relation between tumours occurring in psoriasis and the target mechanism of IL-23 antagonism has been performed and based on literature and own non-clinical data on IL-23 inhibition discussed in the 2.4 Nonclinical Overview, there is no missing information. The available data are sufficient to conclude that there are no specific risks identified, neither with this mechanism of action, nor with skin cancer forms associated with psoriasis, that would add to any perceived concern of change in cancer risk that might stem from modulation of immune function in general.

Safety concerns
Important identified risks: None
Important potential risks: None
Important missing information: None

Part II: Module SIII - Clinical trial exposure

Brief overview of development

Tildrakizumab is a high affinity, humanized immunoglobulin G1/kappa (IgG1/κ) antibody that specifically binds to the IL-23p19 subunit and blocks the interaction of human IL-23 with the IL-23 receptor. The tildrakizumab drug product, 100 mg solution for injection is a sterile, preservative-free, solution aseptically filled into a ready-to-use 1 mL single-dose prefilled glass syringe with staked needle closed with a plunger stopper. The proposed dose is 100 mg although in patients with certain characteristics (e.g., high disease burden, body weight ≥ 90 kg) 200 mg (two 100 mg syringes) may be given for better efficacy.

The clinical development program included evaluations of tildrakizumab (also known as MK-3222 and SCH900222) across 9 completed trials: 6 Phase 1 trials (P05382, P05661, P05776, P05839, P06306, and P009); one Phase 2b trial (P05495; also known as P003); and two Phase 3 trials (P010 and P011).

The Phase 1 trials enrolled healthy subjects (P05661, P05776, and P06306), subjects with moderate-to-severe plaque psoriasis (P05382 and P009), and subjects with active Crohn's disease (P05839). The Phase 2b and Phase 3 trials were conducted in the target subject population with moderate-to-severe chronic plaque psoriasis.

The Phase 2b/3 clinical development program in support of the safety of tildrakizumab includes 3 trials: 1 Phase 2b trial (P05495/P003) and 2 Phase 3 trials (P010 and P011).

Each of the 3 clinical trials was a randomized, double-blind, placebo-controlled, multi-centre, trial conducted in adult patients with chronic plaque psoriasis who were 18 years of age or older and were candidates for phototherapy or systemic therapy.

The Phase 2b trial (P05495/P003) was a dose-finding trial designed to identify the optimal SC dosing regimen for tildrakizumab as measured by the proportion of subjects with at least 75% improvement from Baseline in the Psoriasis Area and Severity Index (PASI 75). Doses of 5 mg, 25 mg, 100 mg, and 200 mg were evaluated. The trial consisted of a 2-part treatment period (Part 1: 16-week, placebo-controlled treatment period; Part 2: 36-week, double-blind, treatment period to evaluate the optimal dose regimen for maintenance of response) and a 20-week follow-up period.

The Phase 3 trials (P010 and P011) consisted of a base treatment period including 3 parts (Part 1: 12-week double-blind, placebo-controlled treatment period; Part 2: 16-week double-blind treatment period to evaluate the maintenance of response; Part 3: 36-week [P010] and 24-week [P011] treatment period to evaluate the long-term efficacy and safety/tolerability of tildrakizumab).

An optional long-term safety extension period (up to 4 years) and a 20-week follow-up period were also employed in the Phase 3 trials and are currently ongoing. In P011, tildrakizumab was also evaluated versus etanercept (Enbrel®), a current standard of care.

For the purposes of the safety assessment in this RMP, the Phase 2 and Phase 3 base period safety pool has been considered. There are two other safety pools (Phase 2 and Phase 3 placebo-controlled safety pool and Phase 3 extension safety pool) that are briefly discussed below and more extensively in the 2.7.4 (see Module 2.7.4.1.1.3.2).

Phase 2 and Phase 3: Base Period Safety Pool

This safety pool supports the exposure-adjusted summary of AEs for the base period. It includes pooled data for the Phase 2 and Phase 3 base periods (52 weeks for P05495/P003 and P011, and 64 weeks for P010) across trials and treatment groups, and the presentation of treatment arms for the purposes of the RMP is as follows: tildrakizumab 5 mg, tildrakizumab 25 mg, tildrakizumab

100 mg, tildrakizumab 200 mg and placebo. In addition, etanercept is presented for P011 only. For this safety pool, subjects with multiple treatments due to trial designs were counted in each treatment received, after adjustment for exposure. For subjects who dropped out during the base period or did not enter the extension period and entered the 20-week follow-up period, AEs occurring during follow-up were included for these subjects and were attributed to the last treatment received.

Phase 2 and Phase 3: Placebo-controlled Safety Pool

This safety pool is used to make comparisons between tildrakizumab and placebo over the placebo-controlled period (16 weeks for P05495/P003 and 12 weeks for P010 and P011). Data are pooled across trials and treatment groups. This dataset is not included in the RMP, however is discussed more extensively in Module. 2.7.4 Summary of Clinical Safety.

Phase 3: Extension Safety Pool

This safety pool supports the assessment of long-term safety and tolerability of tildrakizumab. It includes the pooled Phase 3 extension data up to the targeted cut-off dates of 12-Jun-2016 (P010) and 21-Jun-2016 (P011). Tildrakizumab 200 mg and tildrakizumab 100 mg were pooled across trials. For subjects who dropped out during the extension period and entered the 20-week follow-up period, AEs occurring during the follow-up period were included and were attributed to the last treatment received. This dataset is not included in the RMP, however is discussed more extensively in Module 2.7.4 Summary of Clinical Safety.

Clinical Trial Exposure

Cumulative Subject Exposure in Development Program (all available data until 08 Oct 2023).

Overall, in the completed Merck trials (completed Phase 1 trials [P05382, P05839, P06306, P05661 {P004}, P05776 {P005}, and P009]; completed Phase 2 trial [P05495]; and base portion of the Phase 3 trials [P010 and P011]), a total of 2455 subjects were randomized and treated in the tildrakizumab clinical program, of which 2190 subjects received tildrakizumab.

Overall, in the Sun Pharmaceutical Industries Ltd trials, an additional 391 subjects enrolled in the CLR_16_23 trial; 303 in the CLR_18_07, who had rolled over from the CLR_16_23 trial; 506 in the P010 extension phase; 730 subjects in the P011 extension phase; 231 subjects in the TILD-18-20 (SCALP) trial; 270 subjects in the TILD-19-07 trial (INSPIRE 1); 237 subjects in the TILD-19-19 trial (INSPIRE 2); 22 subjects in the post-marketing interventional TILD-19-12 trial; 99 subjects in TILD-18-19 (NAIL) trial; 129 subjects in the extension trial TILD-21-01; and 220 in the Tildra-PsO-001 extension phase.

In the Almirall trials, 103 subjects in the M-14745-41 (TRANSITION) trial, 177 subjects in the M-14745-42 (TRIBUTE) trial, and 42 subjects in the M-17878-01 trial were enrolled.

It is estimated that 4499 subjects have received tildrakizumab and 662 subjects have received placebo in the Sun Pharmaceutical Industries Ltd clinical trial program, which includes the completed Tildra-PsO-001 study (in the Chinese population). A total of 322 subjects received tildrakizumab in the Almirall clinical trial program. Estimates of overall cumulative subject exposure are provided in Table 2, based upon actual exposure data from completed trials and randomization schemes in ongoing trials.

Table 2. Part II: Module SIII: Cumulative Subject Exposure in the Development Program[a]

Treatment	Number of Subjects[b]
Merck and Sun Pharma Clinical Trial Program	
Tildrakizumab	4499[c]
Placebo	662[d]
Etarnercept	314
Almirall Clinical Trial Program[e]	
Tildrakizumab	322

Data sources: Study clinical study reports (CSRs)
a) Includes subjects and healthy volunteers as of 08 October 2023.
b) Includes subjects who have received tildrakizumab and comparators from both completed and ongoing studies.
c) Includes placebo subjects who received tildrakizumab in Part 2 of the Phase 2 trial (P05495). Also includes estimated exposure from the TILD-19-07, TILD-19-12, and TILD-19-19 trials based on randomization ratios, as trials are ongoing and blinded, as well as subjects who received placebo in the first 24 weeks of the CLR_16_22 and CLR_16_23 trials and tildrakizumab thereafter. No additional subjects are included for CLR_18_07, as this trial includes subjects already counted in the CLR_16_23 trial. Includes subjects in the Tildra-PsO-001 (in the Chinese population). No additional subjects are included for the extension portions of P010, P011, or TILD-21-01, as subjects are already counted in the base portions of these trials.
d) Includes estimated exposure from the TILD-19-07 and TILD-19-19 trials based on randomization ratios, as trials are ongoing and blinded. Includes subjects in the Tildra-PsO-001 (in the Chinese population).
e) Includes estimated exposure from the interventional Almirall clinical trial program.

The cumulative exposure to tildrakizumab by age, sex, and racial group from completed studies is provided in tables 3 and 4.

Table 3. Part II: Module SIII: Cumulative Subject Exposure to Tildrakizumab from Completed Clinical Trials by Age and Sex[1]

Number of Subjects			
Age Range (year)	**Male**	**Female**	**Total**
≤18[2]	9	4	13
19 to 65	2050	951	3001
66 to 75	110	65	175
>75	15	11	26
Total	2184	1031	3215

1 Data from completed trials as of 08 October 2023: Completed trials Phase 1 (P05382, P05839, P06306, P05661 [P004], P05776 [P005], and P009); Phase 2 (P05495); base portion of Phase 3 trials (P010 and P011); Phase 2a study (CLR_16_22) in subjects with Active AS or non-radiographic axial spondylarthritis (nr-axSpA), M-17878-01, base phase of trial (Tildra-PsO-001), CLR_16_23, TRIBUTE (M-14745-42) and TRANSITION (M-14745-41).
2 In P05661 [P004] and P05776 [P005] there was one subject in each trial who was 18 years of age. Similarly, in P05495 there were 2 subjects who were 18 years of age and in P010 there were three subjects who were 18 years of age. There was 1 subject withdrawn from base phase of trial (Tildra-PsO-001).

Table 4.Part II: Module SIII: Cumulative Subject Exposure to Tildrakizumab from Completed Clinical Trials by Racial Group [1]

Racial Group	Number of Subjects
Asian	549
American Indian or Alaska Native	1
Black	56
Caucasian	2539
Other	54
Unknown	16
Total	3215

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 from the two pivotal Phase 3 trials (P010 and P011) are discussed below Table 5 Part II: Module SIV.

Table 5 Part II: Module S IV: Discussion of exclusion criteria and implications for missing information

Criteria	Reason for being an exclusion criterion	Is it considered as missing information? Rationale if not included as missing information
Presence of predominantly non-plaque forms of psoriasis	To avoid confounding of therapeutic indication.	No No difference in safety profile is expected in these patients it is therefore not included as missing information
Subjects with current or history of severe psoriatic arthritis and well-controlled on current therapy	To avoid confounding of therapeutic indication.	No No difference in safety profile is expected in these patients it is therefore not included as missing information
Subjects expected to require topical therapy, phototherapy, or systemic therapy for psoriasis during the trial	To avoid confounding of therapeutic indication	No Exclusion not relevant for routine medical practice
Presence of any infection or history of recurrent infection requiring treatment with systemic antibiotics within 2 weeks prior to screening	Increased risk of serious infections is a potential class effect of immunomodulator therapy	No Serious infections is included as a potential risk in the RMP There are appropriate risk minimization activities in the product information for the management of infections
Presence of severe infection (e.g., pneumonia, cellulitis, bone, or joint infections) requiring hospitalization or treatment with intravenous antibiotics within 8 weeks prior to screening	Increased risk of serious infections is a potential class effect of immunomodulator therapy	No Serious infections is included as a potential risk in the RMP There are appropriate risk minimization activities in the product information for the management of infections.

Criteria	Reason for being an exclusion criterion	Is it considered as missing information? Rationale if not included as missing information
Women of childbearing potential who are pregnant, intend to become pregnant (within 6 months of completing the trial), or are lactating	There is limited information from the use of tildrakizumab in pregnant women. It is not known whether tildrakizumab is excreted in human milk. The effect of ttildrakizumab on human fertility has not been evaluated. Therefore, the potential risk for humans is unknown.	Yes Use in pregnancy and lactation is considered as missing information There are appropriate risk minimization activities in the product information
Subjects with a positive human immunodeficiency virus (HIV) test result, hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) test result	For ethical reasons, such patients may have a higher risk of infections or viral reactivation. Increased risk of serious infections is a potential class effect of immunomodulator therapy	No Serious infections is included as a potential risk in the RMP There are appropriate risk minimization activities in the product information for the management of infections
Subjects with a prior malignancy or concurrent malignancy (excluding successfully treated basal cell carcinoma, squamous cell carcinoma of the skin in situ, squamous cell carcinoma with no evidence of recurrence within 5 years, or carcinoma in situ of the cervix that has been adequately treated).	Increased risk of malignancy is a potential immunomodulator class effect	No There is no evidence from the clinical trial programme of an increased risk of malignancy with use of tildrakizumab. Malignancies is included as a potential risk in the RMP
Subjects who have received live viral or bacterial vaccination within 4 weeks prior to baseline or who intend to receive live viral or bacterial vaccination during the trial.	Interaction with live vaccines is a potential immunomodulator class effect	Yes Use in patients receiving recent live vaccination is considered as missing information. There are appropriate risk minimization activities in the product information
Subjects currently participating in another interventional clinical trial or has participated in an interventional clinical trial within 4 weeks prior to screening.	To avoid confounding factors.	No Exclusion not relevant for routine medical practice
Subject or a family member is among the personnel of the investigational site or Sponsor/designee staff directly involved with this trial.	Conflict of interest within the setting of clinical trial	No Exclusion not relevant for routine medical practice
Subject who within 6 months prior to screening has any significant organ dysfunction that places the subject at unacceptable risk for participation in a trial of an immunomodulatory therapy in the judgment of the investigator.	Unjustified safety risk for patient in the setting of a clinical trial as they may have a higher risk of treatment complications	No Exclusion not relevant for routine medical practice

Criteria	Reason for being an exclusion criterion	Is it considered as missing information? Rationale if not included as missing information
Hospitalization due to an acute CV event, CV illness, or CV surgery within 6 months of screening.	Such patients have an increased risk of cardiac events and therefore of clinical complications. This population is typically excluded from clinical trials to avoid confounding factors	No There is no evidence from the clinical trial programme of an increased risk of MACE with use of tildrakizumab. MACE is included as a potential risk in the RMP
Subjects with sustained uncontrolled hypertension (systolic blood pressure of ≥160 mm Hg and/or diastolic blood pressure of ≥100 mm Hg at screening).	Patients with uncontrolled hypertension have increased risk of cardiac events and therefore of clinical complications. This population is typically excluded from clinical trials to avoid confounding factors	No There is no evidence from the clinical trial programme of an increased risk of MACE with use of tildrakizumab. MACE is included as a potential risk in the RMP
Subjects with uncontrolled diabetes	Patients with uncontrolled diabetes have increased risk of diabetes decompensations and therefore of clinical complications. This population is typically excluded from clinical trials to avoid confounding factors.	No There is no evidence from the clinical trial programme of an increased risk of diabetes or diabetes decompensations with use of tildrakizumab. No difference in safety profile is expected in these patients therefore it is not included as missing information
Subjects who in the opinion of the investigator, will not be able to participate optimally in the trial.	Inability of patients to participate optimally in study. Based on high likelihood of treatment non-compliance and medication error.	No Exclusion not relevant for routine medical practice
Subject who, in the opinion of the investigator, has a history of alcohol or drug abuse in the previous year.	Inability of patients to participate optimally in study	No Exclusion not relevant for routine medical practice
Subject with any previous use of tildrakizumab or other IL-23/Th-17 pathway inhibitors, including p40, p19 and IL-17 antagonists	Relevant to clinical trial setting, to avoid confounding of efficacy endpoint	No No difference in safety profile is expected in these patients therefore it is not included as missing information
Subject has received any listed treatment within the indicated washout period prior to randomization.	To ensure that there is no confounding of trial results due to other active substance carry-over	No Exclusion not relevant for routine medical practice
Subject had previously used etanercept.	Relevant to clinical trial setting, to prevent confounding of efficacy end point (Only P11 trial had an active comparator arm)	No No difference in safety profile is expected in these patients therefore it is not included as missing information
Subject is sensitive or allergic to latex.	Relevant to clinical trial setting (P11 trial only)	No Exclusion not relevant for routine medical practice

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

The clinical development programme is unlikely to detect certain types of adverse reactions such as very rare adverse reactions with a frequency of 1:10,000, adverse reactions with a long latency,

or those caused by prolonged or cumulative exposure. However, in clinical trials, there has been no evidence of organ toxicity which suggests a potential toxicity by cumulative dose. No specific effect due to cumulative effect is expected.

Additionally, the Phase 2b and Phase 3 trials, a total of 1994 patients received any dose of tildrakizumab in the base trial period. Patients were exposed for up to a maximum of 64 weeks during the base trial period. These Phase 3 trials were designed to assess the safety and tolerability of tildrakizumab in subjects with moderate-to-severe plaque psoriasis up to 64weeks; each trial included a long-term extension component (up to 4 years) to evaluate long-term safety. These long-term safety extension trials are currently ongoing. Additionally, a cohort study in a psoriasis registry (PASS) is also planned to follow patients for effects of prolonged exposure to tildrakizumab up to 8 years of follow-up.

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

Table 6. Part II: Module SIV : Exposure of special populations included or not in clinical trial development programmes (Base Period)

Type of special population	Exposure	
	Number of patients (N=1994)	Patient Years
Pregnant women [a]	7	4.1
Breastfeeding women	NA	NA
Patients with relevant comorbidities		
Hepatic impairment [b]	90	99.0
Sub populations with genetic polymorphism [c]	NA	NA
Immuno-compromised [d]	8	6.7
Patients with history of infectious diseases [e]	286	309.6
Renal impairment [f]		
No renal impairment	1328	1367.7
Mild renal impairment	609	630.9
Moderate renal impairment	56	60.4
Severe renal impairment	1	0.1
Renal failure	0	0
Cardiac impairment [g]	463	466.6
Psoriasis severity [h]		
PASI > 10 (moderate and severe)	1986	2050.8
PASI <= 10 (mild)	6	6.7
Patients with prior exp. to bio. therapy for psoriasis	361	364.0
Patients with prior conventional systemic therapy	799	827.5

NA=Not Applicable.

(a) Pregnant women were excluded from studies at screening. However, some women became pregnant during the studies. Discontinuation reason due to pregnancy was used to identify these women. (b) Hepatic impairment based on medical history of hepatobiliary disorders (c) Only if any genetic polymorphisms study has been performed. (d) Immunocompromised patients: Patients with concomitant use of any of the drugs included in the following ATCs: L01, or L03A, or L04A. (e) History of infectious diseases based on medical history of infections and infestations. (f) Renal function categorized based on baseline eGFR: normal when eGFR≥90, mild when 60≤eGFR<90, moderate when 30≤eGFR<60, severe

when 15≤eGFR<30 and renal failure when eGFR<15. (g) Cardiac impairment base on medical history of cardiac disorders (h) Moderate and severe psoriasis based on baseline PASI score.

For duration, each priming dose is counted as 4 weeks of exposure and each subsequent dose is counted as 12 weeks. Exposure in patient years -- multiply exposure in weeks by 7 to get exposure in days and divide by 365.25. Base Period for protocol P003 is Week 0 to Week 52, for P010 is Week 0 to Week 64, for P011 is Week 0 to Week 52.

Source: Statistical Report supporting the Risk Management Plan (RMP)- Table 4 and 4_1.

Children

All subjects in the Phase 2b/3 trials were at least 18 years of age, and there have been no clinical trials conducted in the paediatric patient population to evaluate PK, safety, or efficacy. This product is intended to be used in adult patients.

Elderly

Patients aged 18 years or older were included in the clinical trial programme. A total of 175 patient's ≥65 years old (155 patients aged between 65 and 75 and 20 patients ≥75 years old) were included in the base period safety pool. The overall safety profile in patient ≥ 65 years old and ≥75 years old were comparable with younger populations (< 65 years old and < 75 years old respectively). There was a mild increase in the frequency of some adverse events reported in ≥ 65 years old such as hypertension, COPD, atrial fibrillation, basal cell or squamous cell carcinoma of skin, which is expected for elderly population (Source: Statistical Report supporting the Risk Management Plan (RMP)- Tables 5_1, 5_2, 5_3, 5_4).

In the placebo-controlled safety data pool, rates by age group (age < 65 and ≥ of 65 years old) of adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, drug-related AEs and drug-related SAEs were also analysed.

In general, the AE profile was comparable for tildrakizumab, placebo, and etanercept across subgroups, with the exception of drug-related AEs which were reported with a higher frequency in the etanercept group than in the tildrakizumab and placebo groups in a majority of subgroup categories (see 2.7.4 Summary of Clinical Safety - Appendix 2.7.4-3 for more details).

No additional safety concerns were identified in relation to elderly populations.

Pregnant or breast feeding women

Female patients who were pregnant or lactating were excluded from enrolment in the clinical trials. A total of 13 pregnancies occurred across the whole clinical development programme (Base period plus long-term extension period up to 27th May 2017). There were 2 pregnancies reported in the Phase 1 trials (P05661 and P05839), and 11 pregnancies reported in the Phase 2b/3 trials, including 2 subjects in P05495, 5 subjects in P010, and 4 subjects in P011.

Pregnancy outcomes included 6 deliveries of healthy term infants, 6 cases of foetal loss and in one case outcome is not available to date. In relation to the foetal loss there were 4 elective abortions and 2 spontaneous abortions occurring at week 4 and week 8 of the pregnancy in patients who were smokers, one of whom also had a pregnancy history that included an ectopic pregnancy and another miscarriage in addition to 2 full term live births. Use in Pregnancy and Lactation will be considered missing Information for the purposes of this RMP.

Patients with hepatic impairment

No formal trials with tildrakizumab on patients with hepatic impairment have been conducted. Among subjects receiving tildrakizumab during the base period, there were 90 patients with medical history of hepatic impairment in the Phase 2b/3 trials (Source: Statistical Report supporting

the Risk Management Plan (RMP)-Table 4). The AEs observed in these patients were comparable with AEs observed with the overall population. No additional safety concern was identified in this patient group. (Source: Statistical Report supporting the Risk Management Plan (RMP)-Table 8). Patients with significant organ dysfunction (such as significant hepatic dysfunction) were excluded from the clinical trials. No differences in the safety profile are expected populations with severe hepatic impairment beyond their own risk due to basal conditions. However, use in patients with severe hepatic impairment will be considered missing information for the purposes of this RMP.

Patients with renal impairment

No formal trials with tildrakizumab on patients with renal impairment have been conducted. When the renal function is assessed based on the Glomerular Filtration Renal estimation (eGFR) at baseline, there were 1328 patients with normal renal function, 609 patients with mild renal impairment, 56 patients with moderate renal impairment and 1 patient with severe renal impairment. There were no patients with renal failure (Source: Statistical Report supporting the Risk Management Plan (RMP)- Table 4_1). The adverse events reported in patients with mild renal impairment (eGFR: ≥ 60 to ≤ 90) were comparable to those patients with normal renal function (eGFR: > 90). In a similar fashion, the adverse events reported in patient with moderate renal impairment (eGFR: ≥ 30 to ≤ 60) are comparable with those adverse events observed in patient with normal renal function. No additional safety concern was identified on these populations. No adverse events were reported in the only patient with severe renal impairment (eGFR: < 30). (Source: Statistical Report supporting the Risk Management Plan (RMP)-Table5_12, 5_13, 5_14; 5_15; 5_16). Patients with significant organ dysfunction (such as significant renal dysfunction) were excluded from the clinical trials. No differences in the safety profile are expected populations with severe renal impairment beyond their own risk due to basal conditions. However, use in patients with severe renal impairment will be considered as missing information for the purposes of this RMP.

Patients with other relevant co-morbidity

Among subjects receiving tildrakizumab during the base period, there were a total of 463 patients with cardiac impairment and 8 patients who were immunocompromised included in the Phase 2\Phase 3 studies (Source: Statistical Report supporting the Risk Management Plan (RMP)- Table 4). Due to the low numbers of patients who were immunocompromised included in the clinical development programme, use in immunocompromised patients is considered as missing information for the purposes of this RMP.

Patients with a disease severity different from the inclusion criteria in the clinical trial population

All patients in the P2b/P3 trials were considered candidates for systemic therapy. The majority of patients (99.7%) fulfilled the inclusion criteria for the Phase 2b/3 studies of moderate to severe plaque psoriasis. There were 1986 patients with PASI >10, and 6 patients with PASI <= 10 in the base period. In line with the majority of patients enrolled in the clinical development programme the indication is restricted to the treatment of adults with moderate or severe plaque psoriasis (Source: Statistical Report supporting the Risk Management Plan (RMP)-Table 4).

Sub-populations carrying known and relevant polymorphisms

The immunopathogenesis of psoriasis is not fully understood, as it is the result of a complex interaction between genetic, environmental, and immunological factors. At present there are no specific markers or genetic polymorphisms that can accurately predict disease progression and

therapeutic response. Although many efforts have been made to identify psoriasis/psoriatic arthritis (PsA) biomarkers none of them has yet been translated into routine clinical (Vilanova, 2013).

Patients of different racial and/or ethnic origin

In the Ph2b/3 trials, in the base period, race was reported as white in 81.0% of subjects, Asian in 13.9%, Black or African American in 2.4%, multi-racial in 1.6%, American Indian or Alaska Native in 0.1% and Native Hawaiian or Other Pacific Islander in 0.3% and missing for 0.8% (Source: Statistical Report supporting the Risk Management Plan (RMP)- Table 3).

The effects of race/ethnicity on the exposure of tildrakizumab were assessed with a POP PK analysis of densely sampled serum concentrations from Phase 1 and sparse sampling from Phase 2b and Phase 3 trials. Asian race and Hispanic ethnicity had a small-to-modest influence on tildrakizumab exposure. In addition, a dedicated trial was conducted to compare the PK parameter values of healthy White, Japanese, and Chinese subjects. In both the POP PK model and the dedicated trial, the PK parameter values were found to be similar across these races/ethnicities. Subgroup analyses of the Phase 3 trials further support a lack of clinically significant effect on efficacy and safety for many of these subgroups.

When the safety profile is assessed by race or ethnicity, no meaningful differences are observed. (Source: Statistical Report supporting the Risk Management Plan (RMP)- Tables 5_5, 5_6, 5_7, 5_8, 5_9, 5_10, 5_11).

Use after recent vaccination with live vaccines.

Use in patients who have received a live vaccination within the prior 4-week period was a specific contraindication in the clinical development programme. Due to the immunomodulatory nature of the product, use in this population is therefore warned in the Sec. 4.4 of the SmPC and considered as missing information for the purposes of this RMP.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure.

The methodology used for calculation of patient exposure is presented below:

$$\text{Patient Exposure (Patient Treatment Years)} = \frac{\text{Volume sales in mg}}{\text{Number of Units Received in 365 days}}$$

The Ilumetri recommended dose is 100 mg at Weeks 0, 4, and every twelve weeks thereafter. Each syringe contains 1 mL of 100 mg/mL tildrakizumab.

Based on this information, patient exposure has been calculated in terms of Patient Treatment Years (PTY). It is assumed that one patient received six doses of tildrakizumab 100mg/mL injection (600mg) in one year.

SV.1.2 Exposure

CUMULATIVE PATIENT EXPOSURE FROM MARKETING EXPERIENCE

The cumulative (all available sales data till 31 March 2023) worldwide post authorization patient exposure to tildrakizumab worldwide in terms of Patient Treatment Years (PTY) is estimated to be **44,417.**

Table 7 Part II: Module SV: Cumulative Sales and Estimated Patient Exposure to Tildrakizumab

Molecule		**Tildrakizumab**	**Tildrakizumab**
Formulation strength		**injection 100 mg/1 mL pre-filled syringe**	**injection 100 mg/1 mL pre-filled syringe**
Dosage Form (Units)		**100mg/ml (Pack size - 1*100)**	**100mg/ml (Pack size - 2*100)**
No. of units taken		**6**	**6**
Sales figure (units)	**EU & UK**	136,695	4,237
	Switzerland		
	US		
	Australia[#]		
	Japan		
	Israel		
	Canada[$]		

Molecule		Tildrakizumab	Tildrakizumab
Formulation strength		injection 100 mg/1 mL pre-filled syringe	injection 100 mg/1 mL pre-filled syringe
Dosage Form (Units)		100mg/ml (Pack size - 1*100)	100mg/ml (Pack size - 2*100)
No. of units taken		6	6
Sales in (mg)	EU & UK	13,669,500	847,400
	Switzerland		
	US		
	Australia		
	Japan		
	Israel		
	Canada		
Patient Exposure (PTY)	EU & UK	22,783	1,412
	Switzerland		
	US		
	Australia		
	Japan		
	Israel		
	Canada		
Patient Exposure (PTY)		43,004	1,412
Total Patient Exposure (PTY)		44,417	

[#] includes sold packs as well as free packs

[$]Patient exposure of tildrakizumab (commercial use) in Canada

Table SV.1: Exposure table by indication, gender, age group, region

Not applicable.

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

Potential for misuse for illegal purposes

Tildrakizumab is not structurally or pharmacologically related to any drug known to cause abuse or dependence. The product PK and PD characteristics do not suggest any potential effect on CNS that may produce drug dependence. During the clinical development program there have been no AEs that would be indicative of abuse or a dependence potential and no behaviour or withdrawal symptoms were observed after stopping treatment.

Tildrakizumab is not expected to have a potential for misuse as a recreational drug.

Part II: Module SVII - Identified and potential risks

The overall safety profile of tildrakizumab is in line with compounds in the similar therapeutic class interfering with the IL-23-pathway in psoriasis. In general, the incidence of adverse events was low, mostly similar to placebo, similar to or more favourable than the active comparator etanercept and the adverse events were mainly mild in severity.

Tildrakizumab was generally well tolerated in the Phase 1 and 2b PK trials following administration of multiple IV (up to 10 mg/kg) and SC (up to 400 mg) doses. In the Phase 2b/3 efficacy and safety trials involved comparison of both doses 100 mg and 200 mg tildrakizumab, no dose-related trends were seen in terms of AEs, SAEs, drug-related AEs, discontinuation due to AEs, or Tier 1 AEs (Severe infections, malignancies, major cardiovascular events [MACEs], injection site reactions [ISRs], Drug Related Hypersensitivity Reactions) in tildrakizumab 100 mg and 200 mg doses.

Due to the IL-23 pathway blocking mechanism of action and available experience from similar compounds, severe infection, malignancies, MACEs, and hypersensitivity reactions were considered as potential risks. Additionally, Suicidal ideation and Behaviour (SIB) and Inflammatory Bowel Disease (IBD) were also included as potential risks in the RMP of tildrakizumab (Ilumetri) as SIB and IBD have been suggested to be potentially related with use of other monoclonal antibodies indicated for psoriasis.

Potential for harm from overdose

Overdose of the trial medication was defined as any dose higher than the dose specified in the individual trial protocol as described in the individual trial CSRs (Module 5.3.5.1: P05495) (Ref.5.3.5.1: P010) (Ref. 5.3.5.1: P011). A total of 27 subjects experienced 28 events of accidental overdose: 5 subjects randomized to tildrakizumab 100 mg, 13 subjects randomized to tildrakizumab 200 mg, 4 subjects randomized to placebo, and 5 subjects randomized to etanercept 50 mg. None of the accidental overdose events were serious or associated with an AE.

The risk of overdose is considered low with tildrakizumab given the drug product solution for 100 mg/mL injection is a ready-to-use 1 mL single-dose prefilled syringe.

Potential for transmission of infectious agents

Adventitious Agents Safety Evaluation

The safety of tildrakizumab drug substance (DS) with respect to both non-viral and viral adventitious agents has been assessed by the complementary approaches listed below (Sec.3.2.A.3) in accordance with the Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMA/410/01 Rev. 3) and Ph. Eur. 5.2.8.:

1. Generation and testing of cell lines

All cell bank testing results met the predetermined acceptance criteria and confirmed the absence of bacteria, fungi, mycoplasma, adventitious agents, and infectious retroviruses (Sec.3.2.S.2.3.2). Foetal bovine serum was used during the clone selection of the master cell bank (MCB) and the first working cell bank, subsequently, serum was not used in any process steps, including expansion of the MCB and generation of current. Serum will not be used in the generation of future WCBs.

Porcine trypsin was used in the early stages of production-cell-line development. Trypsin was not used in the preparation of the MCB or WCBs or in antibody manufacturing.

2. Selection and procedural control of raw materials to minimize the risks of introducing adventitious agents

No raw materials of human or animal origin are used in the tildrakizumab DS manufacturing process.

To confirm the suitability of all raw materials, the tildrakizumab DS manufacturing site requires that the origin, traceability, and safety of all raw materials are assessed.

The cane sugar-derived sucrose is not animal derived, but it is purified over bone-derived charcoal of animal origin (which is compliant to Note for Guidance on minimizing risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3). There is no risk for BSE infectivity (Sec. 3.2.A.2).

3. Control of the manufacturing process, including testing of the unprocessed bulk for both non-viral and viral agents, and testing of additional process intermediates for microbial contamination

Each cell culture batch is tested at the unprocessed bulk stage for microbial contamination, mycoplasma, minute virus of mice (MVM), and adventitious viruses (in vitro). Negative test results are required for tildrakizumab DS batch release (Sec. 3.2.S.2.4.1).

Additional routine controls are used in the DS manufacturing process to minimise contamination with non-viral agents such as bacteria and fungi.

4. Evaluation of the capacity of the downstream purification process to clear infectious viruses that potentially may be present

Endogenous and adventitious viruses can be cleared by the downstream manufacturing process, which includes chromatography and dedicated viral clearance (VC) steps.

The above four complementary approaches are considered appropriate for the production of a therapeutic protein product using a Chinese hamster ovary (CHO) cell line. The results demonstrate a sufficient level of safety for patients administered with tildrakizumab. No risk for transmission of infection agents is expected with tildrakizumab.

Potential for medication errors

Description of medication errors during the clinical trial programme

During the clinical development programme (Phase 2b and 3), 2217 patients have been participating and Across the Phase 3 program, a total of 48,941 tildrakizumab/tildrakizumab placebo kits and etanercept/etanercept placebo kits were dispensed to subjects.

A total of 27 subjects experienced 28 events of accidental overdose: 5 subjects randomized to tildrakizumab 100 mg, 13 subjects randomized to tildrakizumab 200 mg, 4 subjects randomized to placebo, and 5 subjects randomized to etanercept 50 mg. The most common accidental overdose was due to the patient or family administering an extra dose in error. All these errors seem to be related to the fact that the patients had access to multiple doses for self-administration.

No subject exceeded a single dose of 200 mg at a given time point. A single subject received 400 mg (two 200 mg injections given 2 weeks apart). This would be the highest dose received, although it was not administered at a single time point. None of the accidental overdose events were serious or associated with an AE. All the events were mild in intensity, with the exception of 3 events that were moderate in intensity (intensity was not reported for 4 events). All the events resolved without sequelae.

Preventive measures for the final product(s) being marketed

1. Prevention of wrong prescription or dispensing

There are only two presentations of tildrakizumab, a box containing 1 single pre-filled syringe for single use containing 100 mg/mL and a box containing 2 pre-filled syringes for single use containing 100 mg/mL each. The posology is simple and clearly stated in the SmPC and PIL as 100 mg or 200 mg at weeks 0, 4 and every 12 weeks thereafter.

According to the SmPC tildrakizumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis. The risk of a wrong prescription is very low or negligible.

2. Prevention of wrong administration (route, dose or method)

The following measures have been taken during product development in order to avoid any wrong dose, site or method of administration:

Device mechanism:

The prefilled syringe components include the syringe barrel with staked needle, rigid needle shield and plunger stopper. The safety device components include a needle guard (with guard, body and spring), plunger rod and finger flange (see Figure 1).

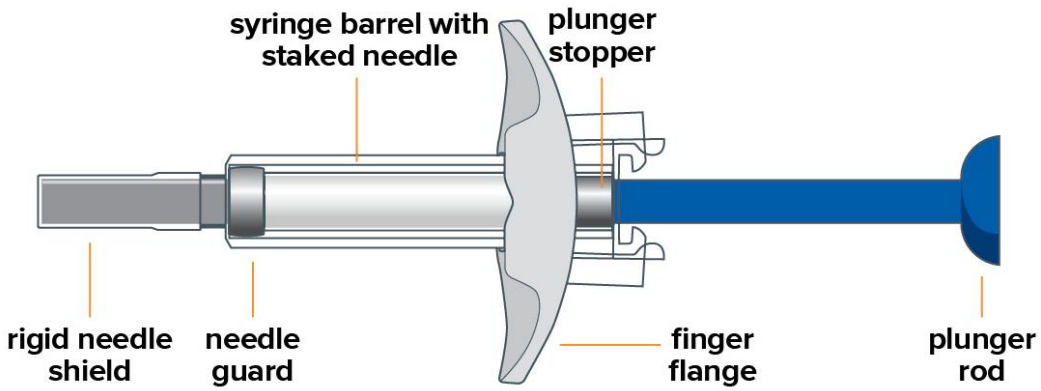

Figure 1. Combination product consisting of tildrakizumab solution in prefilled syringe assembled with safety device.

The prefilled syringe operates by inserting the entire needle perpendicularly into the injection site and pressing the plunger all the way down to initiate the injection and deliver the complete dose. A complete dose is administered if the blue plunger cannot go any further, and there are no spills. After the drug is delivered, the administrator removes the syringe from the injection site and releases the plunger to retract/lock the needle safely into the needle guard.

With this mechanism, the user of the prefilled syringe knows when the total dose has been administered and also the fact that the needle goes inside the needle guard prevents the user using the syringe again.

Information provided in the SmPC/PIL:

- SmPC states that tildrakizumab could be administered by patients after training in the subcutaneous injection technique and if the healthcare professional determines that it is appropriate.
- The full instructions, including pictures for use, are provided in the package leaflet.
- It is specified in the PL what the patient should do in case they use more product than they should or forget to use it.

To confirm that these measures reduce the risk of medication errors a formative human factors study for tildrakizumab prefilled syringe supplied with a commercially available needle safety device was conducted to assess use-related risks of the product's user interface. The user interface tested included the syringe and safety device, instructions for use, and packaging. The study was conducted with participants representing patients as well as Healthcare Professionals (HCP). The formative study results demonstrated that the hazards associated with use of the product have been successfully controlled, such that the product can be used safely by the intended users (i.e., adult patients and healthcare providers), uses, and use environments (Sec.3.2.P.2.2.4).

Effect of device failure

The device risk management and design control planning performed during the development, together with the results from the design verification and validation activities, allows to conclude that the final design for the tildrakizumab prefilled syringe with safety device DP is fit-for-purpose (Sec. 3.2.P.2.2.4).

During the clinical development programme (Phase 2b and 3), 2217 patients have been participating and Across the Phase 3 program, a total of 48,941 tildrakizumab/tildrakizumab placebo kits and etanercept/etanercept placebo kits were dispensed to subjects. Only 2 isolated device failures without associated AEs have been reported: one device occlusion and one device dislocation, both assessed as non-serious and without any associated adverse reaction to the device failure. The effect of device failure is considered negligible and does not impact the safety of the patients.

Potential for PK/PD interactions

No drug interactions with tildrakizumab are anticipated, tildrakizumab is catabolised by general protein degradation processes. A clinical pharmacology study, administering 200 mg of tildrakizumab subcutaneously demonstrated that tildrakizumab does not have a clinically relevant effect on cytochrome P450 enzymes.

Risk of teratogenicity

There was a total of 13 pregnancies across the whole clinical development programme. See section SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes of the RMP for experience of tildrakizumab use in pregnancy during the clinical development program. Animal studies do not indicate a direct or indirect harmful effect with respect to reproductive toxicity, however as a precautionary measure, it is prefereable to avoid the use of Ilumetri during pregnancy. There are appropriate risk minimisation activities suggested

in the SmPC and PIL to reduce the risk of teratogenicity. Use in Pregnancy and Lactation will be considered missing Information for the purposes of this RMP.

Risk to fertility

The effect of Ilumetri on human fertility has not been specifically evaluated, however animal studies do not indicate direct or indirect harmful effects with respect to fertility. There are appropriate risk minimisation activities suggested in the SmPC and PIL to reduce any risk to fertility.

Risk associated with disposal

There are no specific risks associated with disposal and any unused medicinal product or waste material should be disposed of in accordance with local requirements. There are appropriate risk minimisation activities suggested in the SmPC and PIL to ensure appropriate disposal.

Potential for off-label use

The SmPC clearly states that the proposed indication for tildrakizumab is '*Treatment of adults with moderate -to- severe plaque psoriasis who are candidates for systemic therapy'.*

There are to date no known experimental uses of tildrakizumab for other indications. Clinical development activities in relation to a psoriatic arthritis indication are currently planned. It is not expected that tildrakizumab will be used for a non-authorised indication for which there are already therapeutic options available in the market. Nevertheless, potential off-label use during the post-marketing period will be monitored using routine pharmacovigilance measures and will be reported in periodic reports as applicable. The potential for off-label use in the paediatric population is specifically discussed below.

The PIP (EMEA-001451-PIP01-13) was agreed on the 6th March 2014 (EMA decision P/0058/2014). The PIP acknowledges that the overall prevalence of paediatric psoriasis is very low (0.7%): the prevalence in children 0-9 years is 0.37% and 1.01% in children age 10-19 years of age (Augustin M, 2010) According to a population based study in the UK, the prevalence in the paediatric population is 0.55% in the age group 0-9 years and 1.37% in the 10-19 years (Gelfand, 2005b). Given the low prevalence of psoriasis in children aged 10-19 years and extremely low prevalence in children aged 0-9 years there is minimal potential for off-label use in children and adolescents. Topical agents are usually sufficient to control disease in children and there are already other biological agents for example etanercept and adalimumab, authorized in the EU for the treatment of psoriasis in children.

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

Table 8. Part II: Module SVII: Safety concerns in the initial RMP submission - Summary of safety concerns

Important identified risks	None
Important potential risks	Hypersensitivity Serious infections Malignancies Major adverse cardiac events Suicidal Ideation Behaviour (SIB) Inflammatory Bowel Disease (IBD)
Missing information	Safety in pregnant and lactating women Long-term safety Use after recent vaccination with live bacterial or live viral vaccines Use in immunosuppressed patients Use in patients with severe hepatic impairment Use in patients with severe renal impairment

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

There is either no associated relevant risk that impacts the risk-benefit profile for the product or the risk is considered to be minimal in relation to severity of the indication for all the risks below:

- The gastrointestinal disorders of **gastroenteritis, nausea** and **diarrhoea** are adverse reactions listed in Sec. 4.8 of the SmPC. They are not associated with any relevant risks.
- **Back pain** is an adverse reaction listed in Sec. 4.8 of the SmPC, but it is not associated with a relevant risk.
- **Injection site reactions** are considered to be of minimal risk in relation to the severity of the indication being treated.
- The risk of "**neutrophil count decreased**" may have clinical consequences but occurring with a low frequency and considered acceptable in relation to the severity of the indication being treated
- **Upper respiratory tract infections** is an adverse reaction listed in Sec. 4.8 of the SmPC and it is related to the existing risk 'Serious infections'.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

The following risks are considered to have minimal clinical impact on patients and do not impact the risk-benefit profile of the product:

- **Gastroenteritis, nausea, diarrhoea** and **back pain** are commonly occurring ADRs. They are not considered to be serious and not associated with risks that impact the risk-benefit of the product. All events reported were non-serious. They are adequately

captured in Sec. 4.8 of the SmPC as an ADR and are followed up via routine pharmacovigilance.

- **Injection site reactions** are considered to be of minimal clinical impact in relation to the severity of the indication being treated for the following reasons:
    - In studies P003, P010 and P011, for the base period safety pool, the incidence rate of patients with injection site reaction TEAEs was higher with tildrakizumab than placebo. The incidence rates reported were as follows; 1/42 (2.4%) in the tildrakizumab 5 mg group, 1/123 (0.8%) in the tildrakizumab 25 mg group, 34/1081 (3.1%) in the tildrakizumab 100 mg group, 42/1039 (4.0%) in the tildrakizumab 200 mg group, 62/313 (19.8%) on etanercept and 11/588 (1.9%) in the placebo group (Source: Statistical report supporting RMP Table 13_5).
    - All events were non-serious. No events were considered to be severe; all events were either mild or moderate (Source: Statistical report supporting RMP Tables13_5, 15_5).
    - Hence, whilst injection site reactions occurred more frequently compared to placebo, all the events were non-serious. They had a minimal clinical impact on patients and are considered as acceptable in relation to the severity of the indication being treated.

The following risk may have clinical consequences but occurring with a low frequency and considered acceptable in relation to the severity of the indication being treated:

- **Neutrophil count decreased** has been reported with other biologics acting in the same pathway and has been considered a potential risk for some of them. However, in the development project of tildrakizumab the review of the AEs for Neutropenia, Febrile neutropenia, Neutrophil count decreased, Leukopenia and WBC decreased showed a very low frequency of reports, none of which were classed as serious; furthermore, when looking at the laboratory results only a few isolated occurrences of neutropenia were recorded. Therefore, it is an adverse event that may have clinical consequences but occurring with a low frequency and considered acceptable in relation to the severity of the indication being treated.
    - In studies P003, P010 and P011, for the exposure adjusted base period safety pool, there were 3 events in the tildrakizumab 100 mg group, a single event of febrile neutropenia (1/1083) which was associated with underlying acute myeloid leukaemia (AML) (0.10 per 100 subject years) and 2 events of neutropenia (2/1083) (0.20 per 100 subject years). There were 2 events of neutropenia in the tildrakizumab 200 mg group (2/1041) (0.22 per 100 subject years). There were no cases of neutrophil count decreased in either the tildrakizumab 100 or 200 mg groups. There were no events in the etanercept or placebo group (Source: Analyses of clinical studies D121-Table 2).
    - All events were non-serious.
    - There were no drug-related adverse events of neutropenia, febrile neutropenia or neutrophil count decreased.
    - Non-clinical data shows that specific inhibition of the IL-23p19 pathway has a decreased infection liability compared to other immunomodulatory agents (i.e.,

anti-TNF and anti-IL-12/23p40 mAbs). Repeat-dose toxicity studies in cynomolgus monkeys (Sec.2.6.6.3) show no evidence of autoimmune or inflammatory adverse effects or any adverse effects on lymphoid tissues, and therefore not associated with cause for immunotoxicity concern.

- Hence, although neutropenia (as reviewed using PT search terms for Neutropenia, Febrile neutropenia and Neutrophil count decreased) occurred more frequently compared to placebo the number of events is considered low with low clinical impact. All the events were non-serious and were not drug related, which had a minimal clinical impact on patients and are considered as acceptable in relation to the severity of the indication being treated.
- In addition, the undesirable clinical outcome as a consequence of neutropenia is captured and monitored under the potential undesirable clinical outcome of serious infection in line with the current applicable guideline for RMP (EMA/PRAC/613102/2015).

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

Important potential risks were selected based on review of tildrakizumab's characteristics (PK and PD), non-clinical and clinical safety data. Tildrakizumab is a new mAb with a new mechanism of action. It specifically binds to the p19 protein subunit of IL-23 cytokine and inhibits its interaction with the IL-23 receptor. The safety profiles of other products in the same / similar class i.e: mAbs which also interfere at various points in the psoriasis pathogenic pathways have been considered. References are made to the anti-IL-17 agents such as secukinumab and ixekimumab, and to ustekinumab, which is specific for the p40 subunit shared for both IL-12 and IL-23. There are no important identified risks.

The important safety concerns for tildrakizumab are listed below:

Important Identified Risk

- None

Important potential Risks

- Important Potential risk 1: **Hypersensitivity**

  Scientific evidence

  Treatment with monoclonal antibodies may lead to the development of serious anaphylactic or anaphylactoid hypersensitivity reactions. Pooled safety data from clinical development studies P003, P010 and P011 showed that the observed incidence of hypersensitivity TEAEs for patients on tildrakizumab was similar to placebo.

  Risk-Benefit impact

  As the observed incidence of hypersensitivity TEAEs for patients on tildrakizumab was similar to placebo and all the events were non-serious, hypersensitivity is considered as a potential risk and will be further assessed in on-going studies and in post-marketing setting. It can be adequately managed by appropriate risk minimisation activities in the product information; hence the risk-benefit impact is acceptable.

- Important Potential risk 2: **Serious infections**

Scientific evidence

Tildrakizumab has an immunomodulatory mode of action and therefore may be associated with infections. Pooled safety data from the clinical development studies P003, P010 and P011 showed that the exposure adjusted incidence rates of serious infections and infestations (based on SOC TEAEs) for patients on tildrakizumab was similar to placebo.

Risk-Benefit impact

As the exposure adjusted incidence rates for serious infections and infestations were similar for tildrakizumab and placebo, serious infection is considered as a potential risk and will be further assessed in on-going studies and in the post-marketing setting. It can be adequately managed by appropriate risk minimisation activities in the product information; hence the risk-benefit impact is acceptable.

- Important Potential risk 3: **Malignancies**

Scientific evidence

Tildrakizumab has an immunomodulatory mode of action and therefore may be associated with malignancy. Pooled safety data from clinical development studies P003, P010 and P011 showed that exposure adjusted incidence rates for malignancy TEAEs were similar for patients on tildrakizumab to placebo.

Risk-Benefit impact

As the exposure adjusted incidence rates for malignancies were similar for tildrakizumab and placebo, malignancies are considered as a potential risk and will be further assessed in on-going studies and in the post-marketing setting; hence the risk-benefit impact is acceptable.

- Important Potential risk 4: **Major adverse cardiac events (MACE)**

Scientific evidence

Pooled safety data from the clinical development studies P003, P010 and P011 showed that exposure adjusted incidence rates for MACE TEAEs were similar for patients on tildrakizumab to placebo.

Risk-Benefit impact

As the exposure adjusted incidence rates for MACE TEAEs were similar for tildrakizumab and placebo, and there were no serious and related events, MACE is considered as a potential risk and will be further assessed in on-going studies and in the post-marketing setting hence the risk-benefit impact is acceptable.

- Important Potential risk 5: **Suicidal ideation behaviour (SIB)**

Scientific evidence

Safety data from across the entire clinical development programme for tildrakizumab showed a total of 6 cases of SIB.

Risk-Benefit impact

There was a total of 6 SIB cases across the entire clinical development programme for tildrakizumab, with no evidence of relatedness, all cases had confounding factors. Hence, SIB

is considered as a potential risk and will be further assessed in on-going studies and in the post-marketing setting; the risk-benefit impact is acceptable.

- Important Potential risk 6: **Inflammatory Bowel Disease (IBD)**

Scientific evidence

Limited evidence. Safety data from across the entire clinical development programme for tildrakizumab showed a total of 1 case of IBD (reported as Crohn´s disease). The risk was observed with biologicals for which MoA is IL-17 inhibition (different than tildrakizumab).

Risk-Benefit impact

There was a total of one IBD case across the entire clinical development programme for tildrakizumab, with no evidence of relatedness. Hence, IBD is considered as a potential risk and will be further assessed in on-going studies and in the post-marketing setting; the risk-benefit impact is acceptable.

Missing information

- Missing Information 1: **Safety in pregnant and lactating women**

Evidence Source

Pooled data from clinical development studies P003, P010 and P011 shows that very small numbers of pregnant women were exposed to tildrakizumab and the product is not contraindicated in this population.

Risk-Benefit impact

Use in pregnancy/lactation is considered as requiring further characterisation due to the very low numbers of pregnant patients exposed to tildrakizumab in the clinical development programme. The population will be further characterised post-authorisation. Adequate risk minimisation activities are included in the product information; hence the risk-benefit impact is acceptable.

- Missing Information 2: **Long-term safety**

Evidence Source

Up to 64 weeks of safety data is available from the base period and long-term extension data will provide safety data for up to 4 years. It is expected that patients will continue on long-term treatment with tildrakizumab, hence further long-term follow-up of patients will be undertaken.

Risk-Benefit impact

Long-term safety is considered as requiring further characterisation as there is currently limited data on long-term safety available from the Phase 2b/3 clinical trials and long-term extension studies. Long-term safety will be further characterised post-authorisation via the registry-based study, hence the risk-benefit impact is acceptable.

- Missing Information 3: **Use after recent vaccination with live bacterial or live viral vaccines**

Evidence Source

No data is available in this population from clinical development studies P003, P010 and P011 and use of the product is not contraindicated in this population.

Risk-Benefit impact

Use after recent vaccination with live bacterial or live viral vaccines was a contraindication in the clinical development programme for tildrakizumab; hence no data is available in this population. Use after recent vaccination with live vaccines is considered as missing information. Adequate risk minimisation activities are included in the product information; hence the risk-benefit impact is acceptable.

- Missing Information 4: **Use in immunosuppressed patients**

Evidence Source

Pooled data from clinical development studies P003, P010 and P011 shows that very small numbers of immunocompromised patients were exposed to tildrakizumab and the product is not contraindicated in this population.

Risk-Benefit impact

As very few patients who were immunocompromised were included in the clinical development programme for tildrakizumab, use in this population is considered as missing information. Adequate risk minimisation activities are included in the product information; hence the risk-benefit impact is acceptable.

- Missing Information 5: **Use in patients with severe hepatic impairment**

Evidence Source

No formal trials with tildrakizumab on patients with hepatic impairment have been conducted and patients with significant organ dysfunction (such as significant hepatic dysfunction) were excluded from the clinical trials. Among subjects receiving tildrakizumab during the base period, there were 90 patients with a medical history of hepatic impairment in the Phase 2b/3 trials (Source: Statistical Report supporting the Risk Management Plan (RMP)-Table 4).

Risk-Benefit impact

As patients with significant organ dysfunction (such as significant hepatic dysfunction) were excluded from the clinical trials, the use of tildrakizumab in patients with severe hepatic impairment is considered missing information. Adequate risk minimisation activities are included in the product information; hence the risk-benefit impact is acceptable.

- Missing Information 4: **Use in patients with severe renal impairment**

Evidence Source

No formal trials with tildrakizumab on patients with renal impairment have been conducted and patients with significant organ dysfunction (such as significant renal dysfunction) were excluded from the clinical trials. Pooled data from clinical development studies P003, P010 and P011 shows that when the renal function is assessed based on the Glomerular Filtration Renal estimation (eGFR) at baseline, there were 1328 patients with normal renal function, 609 patients with mild renal impairment, 56 patients with moderate renal impairment and 1 patient with

severe renal impairment. There were no patients with renal failure (Source: Statistical Report supporting the Risk Management Plan (RMP)- Table 4_1).

Risk-Benefit impact

As patients with significant organ dysfunction (such as significant renal dysfunction) were excluded from the clinical trials, the use of tildrakizumab in patients with severe renal impairment is considered as missing information. Adequate risk minimisation activities are included in the product information; hence the risk-benefit impact is acceptable.

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

Not applicable

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

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

Important Potential Risk: Hypersensitivity

1. Potential mechanisms:

Treatment with monoclonal antibodies may be associated with the development of antibodies against the therapeutic agent. These antibodies may lead to the development of anaphylactic or anaphylactoid-type reactions. Sensitisation involves primary stimulation and expansion of drug -specific T lymphocytes. This may affect T cells alone or both T cells and B cells with consequent formation of drug-specific antibodies (mostly IgE). After primary sensitisation to a causative drug, a second exposure causes affected T cells and antibodies to enter the elicitation phase, corresponding to the type I to IV immune reactions (Gell and Coombs Classification). Most of the drug allergies observed are type I (IgE-mediated) or IV (T-cell mediated) reactions; type II (IgG-mediated) and III (immune-complex deposition) reactions are only encountered infrequently (Schnyder, 2009).

2. Evidence source(s) and strength of evidence:

Treatment with monoclonal antibodies may lead to the development of serious anaphylactic or anaphylactoid hypersensitivity reactions, therefore hypersensitivity is considered as a potential risk in the RMP. The classification of hypersensitivity as a potential risk is based on evidence from literature (see above "Potential mechanisms") and from the safety profile described for similar mAbs used for psoriasis and from the tildrakizumab clinical development programme. See "Strength of evidence (frequency)" below.

3. Characterisation of the risk:

Frequency:

Table 9. Part II: Module SVII: Incidence of hypersensitivity by Preferred Term in studies P003, P010 & P011 for the base period safety pool

TEAE of Interest Preferred term	Tildrakizumab 5 mg (N=42) n (%) (95% CI)	Tildrakizumab 25 mg (N=123) n (%) (95% CI)	Tildrakizumab 100 mg (N=1081) n (%) (95% CI)	Tildrakizumab 200 mg (N=1039) n (%) (95% CI)	Etanercept (N=313) n (%) (95% CI)	Placebo (N=588) n (%) (95% CI)
Total number of patients with any AEs	0	0	5 0.5) (0.2, 1.1)	2 0.2) (0.0, 0.7)	0	1 (0.2) (0.0, 0.9)
Angioedema	0	0	0	0	0	1 (0.2) (0.0, 0,9)
Hypersensitivity	0	0	1 (0.1) (0.0, 0.5)	0	0	0
Injection site urticaria	0	0	1 (0.1) (0.0, 0.5)	0	0	0
Lip swelling	0	0	1 (0.1) (0.0, 0.5)	0	0	0
Swelling face	0	0	2 (0.2) (0.0, 0.7)	0	0	0
Swollen tongue	0	0	1 (0.1) (0.0, 0.5)	0	0	0
Urticaria	0	0	3 (0.3) (0.1, 0.8)	2 (0.2) (0.0, 0.7)	0 (0.0, 1.2)	1 (0.2) (0.0, 0,9)

Classifications of adverse events are based on the MedDRA (version 19.0).
Treatment emergent adverse event is defined as any event that occurs on or after the first dose of study drug administration or any pre-existing event which worsened in severity after dosing.
When a patient has multiple adverse events within the same preferred term, the patient will only be counted once for the most serious event with that preferred term within each treatment.
Only TEAEs with start dates in Base period are included. Base period for protocol P003 is Week 0 to Week 52, for P010 is Week 0 to Week 64, for P011 is Week 0 to Week 52.
Source: Statistical Report supporting the Risk Management Plan (RMP)- Table 13_4

In studies P003, P010 and P011, for the base period safety pool, the incidence rate of patients with hypersensitivity TEAEs was similar to placebo, with incidence rates of 0.5% for patients on 100 mg tildrakizumab, 0.2% for patients on 200 mg tildrakizumab and 0.2% for patients on placebo (Source: Statistical report supporting the Risk Management Plan (RMP)-Table 13_4).

Seriousness / outcomes

All TEAEs of Hypersensitivity reported (13 cases in 8 patients) were considered non serious by the investigator and were resolved/resolving. No unknown or death outcomes were reported in any of the treatment groups (Source: Statistical Report supporting the Risk Management Plan (RMP)- Table t13_4 and 14_4).

Severity and nature of risk

Of the 13 reported TEAE's of hypersensitivity, 11 were reported in the tildrakizumab 100 or 200 mg group in the mild and moderate category. Two TEAE's were severe and occurred in the

placebo group: one was urticaria and the other was angioedema. No TEAEs were seen in the tildrakizumab 5mg, 25mg, or etanercept group. Table 10. Part II: Module SVII: Incidence of hypersensitivity TEAEs in the tildrakizumab and placebo group by Preferred Term and Severity in studies P003, P010 & P011 in base period safety pool

describes the incidence of hypersensitivity TEAEs in the tildrakizumab 100 mg, 200 mg and placebo group by Preferred Term and severity.

Table 10. Part II: Module SVII: Incidence of hypersensitivity TEAEs in the tildrakizumab and placebo group by Preferred Term and Severity in studies P003, P010 & P011 in base period safety pool

Preferred Term	Severity		
	Mild	Moderate	Severe
Tildrakizumab 100 mg			
Hypersensitivity	0	1	0
Injection site urticaria	1	0	0
Lip swelling	0	1	0
Swelling face	0	2	0
Swollen tongue	0	1	0
Urticaria	1	2	0
Tildrakizumab 200 mg			
Urticaria	1	1	0
Placebo			
Angioedema	0	0	1
Urticaria	0	0	1

Classifications of adverse events are based on the MedDRA (version 19.0).
Treatment emergent adverse event is defined as any event that occurs on or after the first dose of study drug administration or any pre-existing event which worsened in severity after dosing.
When a patient has multiple adverse events within the same preferred term, the patient will only be counted once for the most severe event (in the order of Unknown, Mild, Moderate, Severe) with that preferred term within each treatment.
Only TEAEs with start dates in Base period are included. Base period for protocol P003 is Week 0 to Week 52, for P010 is Week 0 to Week 64, for P011 is Week 0 to Week 52.
Source: Statistical Report supporting the Risk Management Plan (RMP)-Table 15_4

4. Risk factors and risk groups:

None identified.

5. Preventability:

According to the SmPC, tildrakizumab is contraindicated in patients with a previous serious hypersensitivity reaction. In addition, there are warnings in the SmPC, that if a serious hypersensitivity reaction occurs, tildrakizumab should be immediately discontinued and appropriate therapy initiated.

6. Impact on the risk-benefit balance of the product:

During the base period, the incidence rate of hypersensitivity TEAEs for patients on tildrakizumab was similar to placebo and all the events were non-serious (Source: Statistical report supporting RMP Table 13_4 and 14_4).

There were no relevant serious and related events during the base period (Source: Analyses of clinical studies D121-Table 10). No severe reactions were observed (Source: Statistical report supporting RMP Table 15_4).

Hence hypersensitivity is considered as a potential risk and will be further assessed in the post-marketing setting. The impact on the risk benefit balance of the product is considered low and is expected to remain low in the post-marketing setting as adequate risk minimisation activities are included in the product information.

7. Public health impact:

Given that hypersensitivity reactions were only observed in a minority of patients in the clinical development programme and that incidence was similar to placebo, the public health impact is considered to be low.

Important Potential Risk: Serious infections

1. Potential mechanisms:

Patients with psoriasis are at an increased risk of infection. Wakkee et al postulate that patients with more severe psoriasis may have increased susceptibility to infectious disease due to a combination of higher co-morbidity prevalence, unhealthy life-style factors and a higher low-grade inflammatory state (Wakkee, 2011).

Patients with psoriasis are at an increased risk of infection, the risk is partially attributable to the use of immunomodulatory treatments for psoriasis as discussed above. Treatment with anti-TNFα inhibitors is specifically associated with an increased risk of TB infection or reactivation of TB. TNFα is a cytokine responsible for establishing and maintaining the inflammatory response to infections and formation/maintenance of granulomas (Xie, 2014).

In general, the risk is also partially attributable to the use of immunomodulatory treatments for psoriasis. Therefore, the immunomodulatory effect of tildrakizumab may potentially contribute patients to suffer severe infections.

2. Evidence source(s) and strength of evidence:

The classification of serious infections as a potential risk is based on evidence from the clinical development programme and the safety profile described for similar mAbs that act in the same pathways used for psoriasis.

Animal studies do not suggest that tildrakizumab produces a detrimental effect on the immune system. Tildrakizumab has an immunomodulatory mode of action, therefore serious infection is considered a potential risk in the RMP and will be monitored on-going studies and in the post-marketing setting. See "Strength of evidence (frequency)" below.

3. Characterisation of the risk:

Frequency**:**

Severe infection was defined as infection meeting the regulatory definition of a serious adverse event, or any infection requiring IV antibiotics whether or not reported as a serious adverse event, as per the regulatory definition.

In studies P003, P010 & P011, for the base period safety pool, the incidence of severe infection TEAEs was 1.0% for patients on 100 mg tildrakizumab, 1.4% for patients on 200 mg tildrakizumab and 0.3% for patients on placebo (Source: Statistical Report supporting RMP Table 13_1). However, when the exposure adjusted incidence rates for serious TEAEs in the base period were

considered for the infections and infestations SOC, the incidence rate of TEAEs on tildrakizumab was similar to placebo, 1.00 (per 100 subject years) for 100 mg tildrakizumab, 1.61 (per 100 subject years) for 200 mg tildrakizumab and 0.91 (per 100 subject years) for placebo (Source: Analyses of clinical studies D121-Table 9).

When the exposure adjusted incidence rates for serious and drug-related TEAEs in the base period were considered for the infections and infestations SOC, the incidence rate was also similar to placebo, 0.10 (per 100 subject years) for 100 mg tildrakizumab, 0.65 (per 100 subject years) for 200 mg tildrakizumab and 0.46 (per 100 subject years) for placebo (Source Analyses of clinical studies D121-Table 10).

Table 11. Part II: Module SVII: Incidence of severe infection by Preferred Term in studies P003, P010 & P011 for the base period safety pool

TEAE of Interest Preferred term	Tildrakizumab 5 mg (N=42) n (%) (95% CI)	Tildrakizumab 25 mg (N=123) n (%) (95% CI)	Tildrakizumab 100 mg (N=1081) n (%) (95% CI)	Tildrakizumab 200 mg (N=1039) n (%) (95% CI)	Etanercept (N=313) n (%) (95% CI)	Placebo (N=588) n (%) (95% CI)
Total number of patients with any AEs	0 (0.0, 8.4)	2 (1.6) (0.2, 5.8)	11 (1.0) (0.5, 1.8)	15(1.4) (0.8, 2.4)	3 (1.0) (0.2, 2.8)	2 (0.3) (0.0, 1.2)
Appendicitis	0	0	2 (0.2) (0.0, 0.7)	0	0	0
Arthritis bacterial	0	1 (0.8) (0.0, 4.4)	0	0	0	0
Bone tuberculosis	0	0	0	1 (0.1) (0.0, 0.5)	0	0
Cellulitis	0	0	1 (0.1) (0.0, 0.5)	3 (0.3) (0.1, 0.8)	1 (0.3) (0.0, 1.8)	2 (0.3) (0.0, 1.2)
Diverticulitis	0	0	1 (0.1) (0.0, 0.5)	3 (0.3) (0.1, 0.8)	0	0
Epiglottitis	0	0	1 (0.1) (0.0, 0.5)	1 (0.1) (0.0, 0.5)	0	0
Erysipelas	0	0	1 (0.1) (0.0, 0.5)	0	0	0
Gastroenteritis	0	0	1 (0.1) (0.0, 0.5)	1 (0.1) (0.0, 0.5)	0	0
Gastroenteritis salmonella	0	0	0	1 (0.1) (0.0, 0.5)	0	0
Herpes zoster	0	0	0	1 (0.1) (0.0, 0.5)	1 (0.3) (0.0, 1.8)	0
Pneumonia	0	0	0	1 (0.1) (0.0, 0.5)	0	0
Pyelonephritis	0	0	0	1 (0.1) (0.0, 0.5)	0	0
Sepsis	0	0	0	1 (0.1) (0.0, 0.5)	0	0
Sinusitis	0	1 (0.8) (0.0, 4.4)	3 (0.3) (0.1, 0.8)	0	0	0
Soft tissue infection	0	0		1 (0.1) (0.0, 0.5)	0	0
Stenotrophomonas infection	0	0	1 (0.1) (0.0, 0.5)	0	0	0
Urosepsis	0	0	0	0	1 (0.3) (0.0, 1.8)	0
Wound infection	0	0	1 (0.1) (0.0, 0.5)	1 (0.1) (0.0, 0.5)	0	0

Classifications of adverse events are based on the MedDRA (version 19.0).
Treatment emergent adverse event is defined as any event that occurs on or after the first dose of study drug administration or any pre-existing event which worsened in severity after dosing.
When a patient has multiple adverse events within the same preferred term, the patient will only be counted once for the most serious event with that preferred term within each treatment.
Only TEAEs with start dates in Base period are included. Base Period for protocol P003 is Week 0 to Week 52, for P010 is Week 0 to Week 64, for P011 is Week 0 to Week 52.
Source: Source: Statistical Report supporting the Risk Management Plan (RMP)- Table 13_1

Seriousness/outcomes:

All cases of severe infections were reported as serious, except for 1 case. A non-serious case was reported for cellulitis in the etanercept group.

No TEAEs were seen in the tildrakizumab 5 mg group. There were 2 cases; Stenotrophomonas infection and diverticulitis in the tildrakizumab 100 mg and 200 mg group respectively that were not resolved. There was 1 case of sepsis (not resolved) which resulted in death in the tildrakizumab 200 mg group. This case concerns an elderly patient who received etanercept for 218 days (Part 1 and 2) and then tildrakizumab 200 mg (part 3). Lung adenocarcinoma was diagnosed on day 190 when he was on etanercept. He received chemotherapy (docetaxel and selumetinib). On day 251, he discontinued from the trial on Day 286 and had a fatal AE (sepsis) on Day 441. The subject's last active dose of tildrakizumab 200 mg was on Day 222. All other cases were resolved or resolving.

Severity and nature of risk:

No TEAEs were seen in the tildrakizumab 5 mg group. Of the 35 reported TEAEs of serious infection, 18 were in the mild and moderate category and 17 were in the severe category. The table below shows the incidence of severe infection TEAEs in the tildrakizumab 25 mg, 100 mg, 200 mg, etanercept and Placebo Groups by Preferred Term and severity.

Table 12. Part II: Module SVII: Incidence of severe infection TEAEs in studies P003, P010 & P011 for the base period safety pool by Preferred Term and severity

Preferred Term	Severity			
Severe Infections	**Mild**	**Moderate**	**Severe**	**Unknown**
Tildrakizumab 25 mg				
Arthritis bacterial	0	0	1	0
Sinusitis	0	1	0	0
Tildrakizumab 100 mg				
Appendicitis	0	0	2	0
Cellulitis	0	0	1	0
Diverticulitis	0	1	0	0
Epiglottitis	0	0	1	0
Erysipelas	0	1	0	0
Gastroenteritis	0	0	1	0
Sinusitis	2	1	0	0
Stenotrophomonas infection	0	0	1	0
Wound infection	0	1	0	0
Tildrakizumab 200 mg				
Bone tuberculosis	0	1	0	0
Cellulitis	0	2	1	0
Diverticulitis	0	2	1	0
Epiglottitis	0	0	1	0
Gastroenteritis	0	1	0	0
Gastroenteritis salmonella	0	1	0	0
Herpes zoster	0	1	0	0
Pneumonia	0	0	1	0
Pyelonephritis	0	0	1	0
Sepsis	0	0	1	0
Soft tissue infection	0	1	0	0
Wound infection	0	0	1	0
Etanercept				
Cellulitis	0	0	1	0

Preferred Term	Severity			
Severe Infections	**Mild**	**Moderate**	**Severe**	**Unknown**
Herpes zoster	0	1	0	0
Urosepsis	0	1	0	0
Placebo				
Cellulitis	0	0	2	0

Classifications of adverse events are based on the MedDRA (version 19.0).
Treatment emergent adverse event is defined as any event that occurs on or after the first dose of study drug administration or any pre-existing event which worsened in severity after dosing.
When a patient has multiple adverse events within the same preferred term, the patient will only be counted once for the most severe event (in the order of Unknown, Mild, Moderate, Severe) with that preferred term within each treatment.
Only TEAEs with start dates in Base period are included. Base Period for protocol P003 is Week 0 to Week 52, for P010 is Week 0 to Week 64, for P011 is Week 0 to Week 52.
Source: Statistical Report supporting the Risk Management Plan (RMP)- Table 15_1

4. Risk factors and risk groups:

Patients with concomitant chronic debilitating conditions (such as haematological or lymphoreticular malignancies, organ transplanted patients, severe stages of rheumatoid arthritis or systemic lupus erythematosus) who require concomitant immunosuppressive therapies such as steroids at immunosuppressive doses, methotrexate, immunosuppressant or tumour necrosis factor α (TNFα) antagonists (Fica, 2014).

A recent systemic review showed that there may be a small increased risk of overall infection related to the short-term use of TNFα antagonists in the treatment of psoriasis, the majority of infections were non-serious (97.6%) and were upper respiratory tract infections (Dommasch, 2011).It is well recognised that serious infections including atypical infections like TB have been reported with the use of TNFα inhibitors in psoriasis (Dommasch, 2011).

5. Preventability:

Published literature and professional guidelines acknowledge the emergence of new or reactivated TB infection to be a potential risk associated with use of biologic therapies to treat psoriasis and advocate that all patients be screened for TB risk before initiating immunosuppressive therapies (Doherty, 2008).

The product SmPC includes a contraindication for clinically important active infection (e.g. active tuberculosis). Additionally, the SmPC warns prescribers that patients should be closely monitored if they develop a serious infection and that tildrakizumab must not be given to patients with active tuberculosis. Finally, it also mentions to consider anti-TB therapy prior to initiation of therapy in patients with latent TB.

6. Impact on the risk-benefit balance of the product:

During the base period, the exposure adjusted incidence rates of serious infections and infestations SOC TEAEs was similar for tildrakizumab 100 mg and 200 mg to placebo (Source: Analyses of clinical studies D121-Table 9). During the base period, the exposure adjusted incidence rates of serious and related infections and infestations SOC TEAEs was also similar for tildrakizumab 100 mg and 200 mg to placebo (Source: Analyses of clinical studies D121–Table 10).

Hence serious infection is considered a potential risk and will be further assessed on-going studies and in the post-marketing setting. The impact on the risk benefit balance of the product is considered low and is expected to remain low in the post-marketing setting as adequate risk minimisation activities are included in the product information.

7. Public health impact:

Provided that the SmPC warnings are adhered to by the prescriber, particularly in relation to the management of TB, the public health impact is considered to be low and manageable as this is a prescription only drug.

Important Potential Risk: Malignancies

1. Potential mechanisms:

The biological mechanism explaining the relationship of psoriasis and cancer is unclear and under investigation. Psoriasis is a systemic inflammatory disease characterised by immune dysregulation. It is hypothesised that a dysregulated immune system together with chronic inflammation may lead to mutations in dividing cells and errors in the elimination of malignant cells, leading to an increased risk of cancer especially lymphoproliferative cancers (Prizment, 2011; Bernatzky, 2006; de Visser, 2006).

2. Evidence source(s) and strength of evidence:

The classification of malignancies as a potential risk is based on the safety profile described for similar mAbs used for Psoriasis that act on the same pathways, and evidence from the clinical development programme.

Animal studies for tildrakizumab have shown no increase in carcinogenic risk. Tildrakizumab has however an immunomodulatory mode of action, therefore malignancies are considered as a potential risk in the RMP and will be monitored in on-going studies and in the post-marketing setting. See "Strength of evidence (frequency)" below.

3. Characterisation of the risk:

Frequency**:**

In studies P003, P010 & P011, for the base period safety pool, the incidence of patients with malignancy TEAE's was the highest for the 100 mg and 200 mg tildrakizumab groups, which were reported in 17/1081 (1.6%) patients and 11/1039 (1.1%) patients, respectively. The 25 mg group reported an incidence of 2/123 (1.6%) patients. Malignancy was reported in 4/313 (1.3%) patients for the etanercept group and in 2/588 (0.3%) in placebo group. No incidences were reported for the tildrakizumab 5mg group.

Table 13. Part II: Module SVII: Incidence of malignancies by Preferred Term in studies P003, P010 & P011 for the base period safety pool

TEAE of Interest Preferred term	Tildrakizumab 5 mg (N=42) n (%) (95% CI)	Tildrakizumab 25 mg (N=123) n (%) (95% CI)	Tildrakizumab 100 mg (N=1081) n (%) (95% CI)	Tildrakizumab 200 mg (N=1039) n (%) (95% CI)	Etanercept (N=313) n (%) (95% CI)	Placebo (N=588) n (%) (95% CI)
Total number of patients with any AEs	0 (0.0, 8.4)	2 (1.6) (0.2, 5.8)	17 (1.6) (0.9, 2.5)	11 (1.1) (0.5, 1.9)	4 (1.3) (0.3, 3.2)	2 (0.3) (0.0, 1.2)
Acute myeloid leukaemia	0	0	1 (0.1) (0.0, 0.5)	0	0	0
Basal cell carcinoma	0	1 (0.8) (0.0, 4.4)	7 (0.6) (0.3, 1.3)	5 (0.5) (0.2, 1.1)	2 (0.6) (0.1, 2.3)	1 (0.2) (0.0,0.9)
Bladder Transitional cell carcinoma	0	0	1 (0.1) (0.0, 0.5)	0	0	0
Breast cancer	0	0	0	1 (0.1) (0.0, 0.5)	1 (0.3) (0.0, 1.8)	0
Lung adenocarcinoma	0	0	0	0	1 (0.3) (0.0, 1.8)	0
Malignant melanoma	0	1 (0.8) (0.0, 4.4)	0	0	0	0
Malignant melanoma in situ	0	0	2 (0.2) (0.0, 0.7)	0	0	0
Pancreatic carcinoma	0	0	0	2 (0.2) (0.0, 0.7)	0	0
Rectal cancer	0	0	1 (0.1) (0.0, 0.5)	0	0	0
Squamous cell carcinoma of skin	0	0	6 (0.6) (0.2, 1.2)	3 (0.3) (0.1, 0.8)	0	1(0.2) (0.0,0.9)
Thyroid cancer	0	0	1 (0.1) (0.0, 0.5)	0	0	0

Classifications of adverse events are based on the MedDRA (version 19.0).
Treatment emergent adverse event is defined as any event that occurs on or after the first dose of study drug administration or any pre-existing event which worsened in severity after dosing.
When a patient has multiple adverse events within the same preferred term, the patient will only be counted once for the most serious event with that preferred term within each treatment.
Only TEAEs with start dates in Base period are included. Base period for protocol P003 is Week 0 to Week 52, for P010 is Week 0 to Week 64, for P011 is Week 0 to Week 52.
Source: Statistical Report supporting the Risk Management Plan (RMP)- Table 13_2

When adjusted per exposure, comparable rates per 100 subject-years were also observed between the tildrakizumab 200 mg, tildrakizumab 100 mg, and the placebo group for, malignancies, NMSC, melanoma skin cancer.

Table 14. Part II: Module SVII: Summary of subjects with tier 1 adverse events – Exposure adjusted (based on 20-week follow-up) Phase 2 and 3: Base period safety pool all subjects as treated

With Malignancies[b]		
	n	(m[a])
Placebo	2	(0.91)
Tildrakizumab 100 mg	17	(1.70)
Tildrakizumab 200 mg	11	(1.18)
Tildrakizumab 100 / 200 mg	28	(1.45)
Etanercept 50 mg	2	(1.96)
With Non-Melanoma Skin Cancer		
Placebo	2	(0.91)
Tildrakizumab 100 mg	11	(1.10)
Tildrakizumab 200 mg	8	(0.86)
Tildrakizumab 100 / 200 mg	19	(0.99)
Etanercept 50 mg	2	(1.30)
With Melanoma Skin Cancer		
Placebo	0	(0.00)
Tildrakizumab 100 mg	2	(0.20)
Tildrakizumab 200 mg	0	(0.00)
Tildrakizumab 100 / 200 mg	2	(0.10)
Etanercept 50 mg	0	(0.00)

(m[a]) is the number of subjects with event per 100-subject-year.
[b] Excluding carcinoma in situ of the cervix
Source: 2.7.4 Summary of Clinical Safety- Table 2.7.4-35

Seriousness/outcomes:

All cases for malignancies were considered serious with the exception of 4 basal cell carcinoma cases (1 case in the tildrakizumab 25 mg group, 2 cases in the tildrakizumab 100 mg group and 1 case in the tildrakizumab 200 mg group) which were non serious.

No TEAEs were seen in the tildrakizumab 5mg group or the placebo group. Of the 38 cases, 31 were resolved\resolving. There were 6 cases that were not resolved and 1 case which resulted in death. This death case (P011; AN208400) concerns an adult male on tildrakizumab 100 mg throughout was treated with a bone marrow transplant for acute myeloid leukaemia (AML), who developed a Stenotrophomonas infection and died 15 days after its onset on Day 320. The death was attributed to the AML. The below table shows the Incidence of malignancies in the tildrakizumab 25 mg, 100 mg, 200 mg and etanercept group by Preferred Term and Outcome.

Table 15. Part II: Module SVII: Incidence of malignancies in studies P003, P010 & P011 for the base period safety pool by Preferred Term and Outcome

Malignancy Preferred Term	**Resolved\ Resolving**	**Not resolved**	**Unknown**	**Death**
Tildrakizumab 25 mg				
Basal cell carcinoma	1	0	0	0
Malignant melanoma	0	1	0	0
Tildrakizumab 100 mg				
Acute myeloid leukaemia	0	0	0	1
Basal cell carcinoma	7	0	0	0
Bladder transitional cell carcinoma	1	0	0	0
Malignant melanoma in situ	2	0	0	0

Malignancy Preferred Term	Resolved\ Resolving	Not resolved	Unknown	Death
Rectal cancer	0	1	0	0
Squamous cell carcinoma of skin	6	0	0	0
Thyroid cancer	1	0	0	0
Tildrakizumab 200 mg				
Basal cell carcinoma	5	0	0	0
Breast cancer	0	1	0	0
Pancreatic carcinoma	0	2	0	0
Squamous cell carcinoma of skin	3	0	0	0
Etanercept				
Basal cell carcinoma	2	0	0	0
Breast cancer	1	0	0	0
Lung adenocarcinoma	0	1	0	0
Placebo				
Basal cell carcinoma	1	0	0	0
Squamous cell carcinoma of skin	1	0	0	0

Classifications of adverse events are based on the MedDRA (version 19.0).
TEAE is defined as any event that occurs on or after the first dose of study drug administration or any pre-existing event which worsened in severity after dosing.
When a patient has multiple AEs within the same preferred term, the patient will only be counted once for the event with the worst outcome (in the order of Unknown, Resolved/ Resolving, Not Resolved, Death) with that preferred term within each treatment.
Only TEAEs with start dates in Base period are included. Base Period for protocol P003 is Week 0 to Week 52, for protocol 010 is Week 0 to Week 64, and for protocol 011 is Week 0 to Week 52.
Source: Statistical Report supporting the Risk Management Plan (RMP)-Table 14_2

Severity and nature of risk:

No TEAEs were seen in the tildrakizumab 5mg group or the placebo group. Of the 38 reported TEAEs of malignancies, 27 were in the mild and moderate category. Nine were in the severe category and 2 were in the unknown category.

Table 16 shows the incidence of malignancies in the tildrakizumab 25 mg, 100 mg, 200 mg and etanercept group by Preferred Term and severity.

Table 16. Part II: Module SVII: Incidence of malignancies in studies P003, P010 & P011 for the base period safety pool by Preferred Term and Severity

Malignancy Preferred Term	Severity			
	Mild	Moderate	Severe	Unknown
Tildrakizumab 25 mg				
Basal cell carcinoma	0	1	0	0
Malignant melanoma	0	0	1	0
Tildrakizumab 100 mg				
Acute myeloid leukaemia	0	1	0	0
Basal cell carcinoma	4	3	0	0
Bladder transitional cell carcinoma	0	0	1	0
Malignant melanoma in situ	0	1	0	1
Rectal cancer	0	0	1	0
Squamous cell carcinoma of skin	3	3	0	0

Malignancy Preferred Term	Severity			
	Mild	Moderate	Severe	Unknown
Thyroid cancer	0	1	0	0
Tildrakizumab 200 mg				
Basal cell carcinoma	0	3	2	0
Breast cancer	0	1	0	0
Pancreatic carcinoma	0	0	1	1
Squamous cell carcinoma of skin	0	2	1	0
Etanercept				
Basal cell carcinoma	1	1	0	0
Breast cancer	0	0	1	0
Lung adenocarcinoma	0	0	1	0
Placebo				
Basal cell carcinoma	1	0	0	0
Squamous cell carcinoma of skin	0	1	0	0

Classifications of adverse events are based on the MedDRA (version 19.0).
Treatment emergent adverse event is defined as any event that occurs on or after the first dose of study drug administration or any pre-existing event which worsened in severity after dosing.
When a patient has multiple adverse events within the same preferred term, the patient will only be counted once for the most severe event (in the order of Unknown, Mild, Moderate, Severe) with that preferred term within each treatment.
Only TEAEs with start dates in Base period are included. Base Period for protocol P003 is Week 0 to Week 52, for P010 is Week 0 to Week 64, for P011 is Week 0 to Week 52.
Source: Statistical Report supporting the Risk Management Plan (RMP)- Table 15_2

4. Risk factors and risk groups:

Cancer risk seems to be higher in patients with severe psoriasis (Beyaert, 2013). Patients with long standing psoriasis seem to be at an increased risk for colon, bladder, and kidney cancer (Brauchli, 2009). Patients receiving high dose PUVA and methotrexate for psoriasis are at an increased risk of skin cancer. In a US prospective PUVA follow-up study of patients with severe psoriasis, more than 25% of patients exposed to high doses of PUVA developed squamous cell cancer (SCC): the relative risk of SCC for patients exposed to high dose PUVA was 5.9 (95% CI 4.0-8.7) compared to those exposed to low dose PUVA. High dose methotrexate was determined to be an independent risk factor for developing SCC with a relative risk of 2.1 (95% CI 1.4-2.8) compared to low or no exposure to methotrexate (Stern, 1994).

5. Preventability:

The SmPC for tildrakizumab states that animal carcinogenicity studies have not been conducted with tildrakizumab. Studies in mouse tumour models showed that selective inhibition of IL-23p19 does not increase carcinogenic risk.

6. Impact on the risk-benefit balance of the product:

During the base period, the exposure-adjusted incidence rates for malignancy TEAEs was similar for Tildrakizumab 100 mg and 200 mg to placebo (Source: Summary of clinical safety Table 2.7.4-35). During the base period, the exposure adjusted incidence rates of serious and related neoplasms (benign, malignant and unspecified) SOC TEAEs was also similar for tildrakizumab 100 mg and 200 mg to placebo (Source Analyses of clinical studies D121–Table 10).

Hence malignancy is considered as a potential risk and will be further assessed in on-going studies and in the post-marketing setting. The impact on the risk benefit balance of the product is

considered low and is expected to remain low in the post-marketing setting as adequate risk minimisation activities are included in the product information.

7. Public health impact:

No impact on public health is expected.

Important Potential Risk: Major Cardiovascular Events

1. Potential mechanisms:

Patients with psoriasis are known to have an increased risk of cardiovascular disease, potentially due to the overlapping mechanisms of systemic inflammation. Endothelial dysfunction and uncontrolled inflammation may contribute (Mrowietz, 2006).

The chronic inflammatory response observed in psoriasis with the production of Th1 and Th17 cytokines promotes systemic inflammation. Proinflammatory cytokines such as TNFα and IL-6 may stimulate the hypothalamic-pituitary axis, which is associated with central obesity, hypertension and insulin resistance. Thus, psoriasis may aggravate obesity, diabetes, thrombosis and atherosclerosis. These same conditions with production of inflammatory molecules such as IL-6, TNFα, plasminogen activation inhibitor (PAI-1) and some adipokines (leptin and resistin) may induce a chronic pro-inflammatory state, contributing to the onset and/or worsening of psoriasis (Davidovici, 2010). There is additionally evidence of a dysregulation in gene expression in psoriatic lesions of the metabolic pathways involved in atherosclerosis including pathways involving PPARα, RAR activation, renin–angiotensin signalling and leptin signalling (Suarez-Farinas, 2012).

2. Evidence source(s) and strength of evidence:

Psoriasis patients have an increased risk of cardiovascular events due to overlapping mechanisms of systemic inflammation; therefore, MACE is considered a potential risk in the RMP and will be monitored in on-going studies and in the post-marketing setting.

The classification of MACE as a potential risk is based on evidence from the clinical development programme, the safety profile described for similar mAbs that acts in the same pathways used for psoriasis. See "Strength of evidence (frequency)" below.

3. Characterisation of the risk:

Frequency**:**

Adjudication of major adverse cardiovascular events (MACE) and all deaths was conducted by an external Data Monitoring Committee which confirmed each of these events.
MACE included non-fatal myocardial infarction, non-fatal stroke, and CV deaths that are confirmed as "cardiovascular" or "sudden".

Table 17. Part II: Module SVII: MACE TEAEs by Preferred Term in studies P003, P010 & P011 for the base period safety pool

TEAE of Interest Preferred term	Tildrakizumab 5 mg (N=42) n (%) (95% CI)	Tildrakizumab 25 mg (N=123) n (%) (95% CI)	Tildrakizumab 100 mg (N=1081) n (%) (95% CI)	Tildrakizumab 200 mg (N=1039) n (%) (95% CI)	Etanercept (N=313) n (%) (95% CI)	Placebo (N=588) n (%) (95% CI)
Total number of patients with any AE of interest	0 (0.0, 8.4)	1 (0.8) (0.0, 4.4)	4 (0.4) (0.1, 0.9)	3 (0.3) (0.1, 0.8)	0 (0.0, 1.2)	1 (0.2, 0.9)
Acute myocardial infarction	0	0	1 (0.1) (0.0, 0.5)	0	0	0
Aneurysm	0	0	0	1 (0.1) (0.0, 0.5)	0	0
Cerebellar infarction	0	0	0	0	0	1 (0.2) (0.0, 0.9)
Coronary artery disease	0	0	0	1 (0.1) (0.0, 0.5)	0	0
Ischaemic stroke	0	1 (0.8) (0.0, 4.4)	0	0	0	0
Myocardial infarction	0	0	1 (0.1) (0.0, 0.5)	0	0	0
Respiratory arrest	0	0	1 (0.1) (0.0, 0.5)	0	0	0
Thrombotic cerebral infarction	0	0	1 (0.1) (0.0, 0.5)	0	0	0
Transient ischaemic attack	0	0	0	1 (0.1) (0.0, 0.5)	0	0

Classifications of adverse events are based on the MedDRA (version 19.0).
Treatment emergent adverse event is defined as any event that occurs on or after the first dose of study drug administration or any pre-existing event which worsened in severity after dosing.
When a patient has multiple adverse events within the same preferred term, the patient will only be counted once for the most serious event with that preferred term within each treatment.
Only TEAEs with start dates in Base period are included. Base Period for protocol P003 is Week 0 to Week 52, for P010 is Week 0 to Week 64, for P011 is Week 0 to Week 52.
Source: Statistical Report supporting the Risk Management Plan (RMP)- table 13_3_2

In studies P003, P010 & P011, for the base period safety pool, the incidence of patients with MACE events was reported in 4/1081 (0.4%) and 3/1039 (0.3%) patients from the tildrakizumab, 100 and 200 mg groups, respectively and 1/588 (0.2%) in placebo group. There were no events in the tildrakizumab 5 mg, etanercept.

Exposed adjusted rates have also been calculated, consideration is to be given to the shorter period of time where patients had been on placebo or etanercept arm. Adjusted rates in number of patient per-100 subject-years are detailed in table 18:

Table 18. Part II: Module SVII: Subjects with confirmed composite adjudicated cardiovascular events - Exposure adjusted (based on 20-week follow-up) Phase 2 and 3: Base period safety pool all subjects as treated

	Placebo		Tildrakizumab 100 mg		Tildrakizumab 200 mg		Tildrakizumab 100/200 mg		Etanercept 50 mg	
	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)
Subjects in population†	588		1083		1041		1911		313	
MACE[b]	1	(0.46)	4	(0.40)	3	(0.32)	7	(0.36)	0	(0.00)

n = Number of Subjects with post-baseline test results (or combination of test results from the same day) that met predetermined criteria.
m† = the number of subjects with event per 100-subject-year for Subjects with at least one post-baseline test result or combination of test results from the same day.
†Subjects who took at least one dose of study medication based on the treatment actually received.
[b]Includes non-fatal myocardial infarction, non-fatal stroke, and CV deaths that are confirmed as 'cardiovascular' or 'sudden'.
MACE = Major Adverse Cardiovascular Events.
Source:2.7.4 Summary of Clinical Safety – Table 2.7.4 36

Seriousness/outcomes:

There were no events in the tildrakizumab 5 mg or etanercept groups. All cases in the tildrakizumab 25 mg, 100 mg and 200 mg or in placebo groups were serious. Of the 9 cases, 4 cases were resolved/resolving, 2 were unresolved and 3 resulted in death. The table below describes the incidence of MACE in the tildrakizumab 25 mg, 100 mg, and 200 mg and in placebo groups by Preferred Term and Outcome.

Table 19. Part II: Module SVII: Incidence of MACEs in studies P003, P010 & P011 for the base period safety pool by Preferred Term and Outcome

MACEs **Preferred Term**	**Resolved/ Resolving**	**Not resolved**	**Unknown**	**Death**
Tildrakizumab 25 mg				
Ischaemic stroke	0	1	0	0
Tildrakizumab 100 mg				
Acute myocardial infarction	1	0	0	0
Cerebellar infarction	0	0	0	0
Myocardial infarction	0	0	0	1
Respiratory arrest	0	0	0	1
Thrombotic cerebral infarction	0	1	0	0
Tildrakizumab 200 mg				
Aneurysm	0	0	0	1
Coronary artery disease	1	0	0	0
Transient ischaemic attack	1	0	0	0
Placebo				
Cerebellar infarction	1	0	0	0

Classifications of adverse events are based on the MedDRA (version 19.0).
Treatment emergent adverse event is defined as any event that occurs on or after the first dose of study drug administration or any pre-existing event which worsened in severity after dosing.
When a patient has multiple adverse events within the same preferred term, the patient will only be counted once for the event with the worst outcome (in the order of Unknown, Resolved/ Resolving, Not Resolved, Death) with that preferred term within each treatment.
Only TEAEs with start dates in Base period are included. Base Period for protocol P003 is Week 0 to Week 52, for P010 is Week 0 to Week 64, for P011 is Week 0 to Week 52.
Source: Statistical Report supporting the Risk Management Plan (RMP)- Table 14_3_2

Severity and nature of risk:

There were no events of MACE in the tildrakizumab 5mg or in the etanercept groups. Of the 9 cases, 2 cases were reported in the tildrakizumab 200 mg group in the mild and moderate category. The remaining 7 cases were reported in the severe category. Table 20. Part II: Module SVII: Incidence of MACE in studies P003, P010 & P011 for the base period safety pool by Preferred Term and Severity
5 describes the incidence of MACE in the tildrakizumab 25 mg, 100 mg, and 200 mg and in placebo groups by Preferred Term and Severity.

Table 20. Part II: Module SVII: Incidence of MACE in studies P003, P010 & P011 for the base period safety pool by Preferred Term and Severity

MACEs Preferred Term	**Severity**			
	Mild	**Moderate**	**Severe**	**Unknown**
Tildrakizumab 25 mg				
Ischaemic stroke	0	0	1	0
Tildrakizumab 100 mg				
Acute myocardial infarction	0	0	1	0
Cerebellar infarction	0	0	0	0
Myocardial infarction	0	0	1	0
Respiratory arrest	0	0	1	0
Thrombotic cerebral infarction	0	0	1	0
Tildrakizumab 200 mg				
Aneurysm	0	0	1	0
Coronary artery disease	0	1	0	0
Transient ischaemic attack	1	0	0	0
Placebo				
Cerebellar infarction	0	0	1	0

Classifications of adverse events are based on the MedDRA (version 19.0).
Treatment emergent adverse event is defined as any event that occurs on or after the first dose of study drug administration or any pre-existing event which worsened in severity after dosing.
When a patient has multiple adverse events within the same preferred term, the patient will only be counted once for the most severe event (in the order of Unknown, Mild, Moderate, Severe) with that preferred term within each treatment.
Only TEAEs with start dates in Base period are included. Base Period for protocol P003 is Week 0 to Week 52, for P010 is Week 0 to Week 64, for P011 is Week 0 to Week 52.
Source: Statistical Report supporting the Risk Management Plan (RMP)- Table 15_3_2.

4. Risk factors and risk groups:

Patients with psoriasis are at increased risk of MI and stroke (Armstrong, 2013) and of a major CV event (Parisi, 2015) and this risk appears to increase with severity of disease (Armstrong, 2013; Parisi, 2015, Maxwell, Joseph et al Differential Roles for Interleukin-23 and Interleukin-17 in Intestinal Immunoregulation. Immunity, 2015 Oct 20;43(4):739-50. Mehta, 2011). The increased cardiovascular risk observed in psoriasis may result from a number of often related risk factors including: smoking, obesity, hypertension and alcohol misuse. In addition, the use of dyslipidaemic therapies, such as corticosteroids, acitretin and ciclosporin and an associated unfavourable lipid profile with high triglycerides and low HDL may contribute. Psoriasis itself is an independent risk factor for MACE (Maxwell, Joseph R. et al). Differential Roles for Interleukin-23 and Interleukin-17 in Intestinal Immunoregulation. Immunity, 2015 Oct 20;43(4):739-50. Mehta, 2011) and the overall increased risk may be related to a combination of these factors in the patient (Mrowietz, 2006)

5. Preventability:

The risk will be continuously monitored via the post-marketing registry-based study and via routine pharmacovigilance.

6. Impact on the risk-benefit balance of the product:

During the base period, the exposure-adjusted incidence rate for MACE TEAEs was similar for tildrakizumab 100 mg and 200 mg to placebo (Source: Summary of clinical safety Table 2.7.4-36). Some severe events were observed (Source: Statistical reporting for RMP Table 15_3_2). There were no serious and related events (Source: Analyses of clinical studies D121-Table 10).

Hence MACE is considered as a potential risk and will be further assessed in on-going studies and in the post-marketing setting. The impact on the risk benefit balance of the product is considered low and is expected to remain low in the post-marketing setting.

7. Public health impact:

No impact on public health is expected.

Important Potential Risk: Suicidal ideation behaviour (SIB)

1. Potential mechanisms:

Patients with psoriasis have an increased prevalence of the psychiatric disorders, anxiety, depressive disorders and SIB (Gupta, 1998, Kurd, 2010, Koo 2017). The skin lesions of psoriasis often lead to seclusion which may lead to behavioural disorders. Hence treatment of psoriasis may indirectly potentially also promote improvement of depression (Oliveira, 2015).

2. Evidence source(s) and strength of evidence:

The classification of SIB as a potential risk is based on the safety profile described for similar mAbs used for Psoriasis that act on the same pathways, and on evidence from the clinical development programme.

Psoriasis patients have an increased risk of depression and suicidal ideation. SIB events have been observed with other mAbs used in psoriasis for example brodalumab (anti-IL-17), therefore SIB is considered as a potential risk in the RMP and will be monitored in on-going studies and in the post-marketing setting. See “Strength of evidence (frequency)” below.

3. Characterisation of risk:

Frequency:

There was a total of 6 SIB cases across the entire tildrakizumab clinical development programme including cases identified in the P1 trials, base period and in the long-term extension period (with a data cut-off 27th May 2017).

Frequency during base period:

In studies P003, P010 & P011, for the base period safety pool, SIB TEAEs were reported in 1/1039 (0.1%, [95% CI 0.0-0.5]) patients in the 200 mg tildrakizumab group. There was no incidence of SIB TEAEs reported in the 5 mg, 25 mg, 100 mg tildrakizumab groups, etanercept or placebo groups (Statistical Report supporting the Risk Management Plan Table 13_6).

Frequency during extension period:

In studies P010 & P011, for the extension period safety pool (cut-off date 27th May 2017), SIB TEAEs were reported in 3/620 (0.5%) patients in the 100 mg tildrakizumab group and in 1/616 (0.2%) patients in the 200mg tildrakizumab group (Statistical Report supporting the Risk Management Plan Table_24_6).

Frequency during Phase 1 trials:

In addition, during a Phase 1 trial there was a single event of suicidal ideation described as a situational crisis with suicidal ideation in a subject facing substantial gambling debts and other psychosocial stressors. The event was not considered to be causally related to trial medication by either the investigator or the Sponsor.

Seriousness/outcomes:

Seriousness/outcomes during base period:

During the base period, there was one SIB case (PT: suicide attempt) which was reported as serious (Statistical Report supporting the Risk Management Plan Table 13_6). The case was considered as resolved/resolving (Statistical Report supporting the Risk Management Plan Table 14_6) and reported as severe.

Seriousness/outcomes during extension period:

During the extension period one case of SIB was reported as serious (PT-completed suicide). The remaining 3 SIB cases were all of suicidal ideation and were reported as non-serious (Statistical Report supporting the Risk Management Plan Table 24_6). Of the 3 cases of suicidal ideation, 2 cases were considered as resolved/resolving and one case was considered as not resolved, this patient continued the trial for 198 days and then withdrew by herself. (Statistical Report supporting the Risk Management Plan Table 25_6).

During the extension period, of the 4 events of SIB, 2 were in the mild category and 2 were in the severe category. (Statistical Report supporting the Risk Management Plan Table 26_6).

4. Risk factors and risk groups:

Patients with psoriasis have an increased prevalence of the psychiatric disorders anxiety and depressive disorders (30% and 60% respectively). About 10% of psoriasis patients consider the possibility of suicide (Gupta, 1998). Patients with psoriasis are at a higher risk of depression, suicidal ideation, suicide attempt and completed suicide (Gupta, 1998; Kurd, 2010; Koo, 2017).

5. Preventability:

Given that there is no current evidence of causality of any of the SIB events with tildrakizumab treatment, no risk minimisation measures are currently proposed in the product SmPC/PIL. SIB events will be closely monitored in the post-marketing setting and the need for specific risk minimisation measures in the product information will be periodically assessed in the post-marketing setting.

6. Impact on the risk-benefit balance of the product:

A total of 6 SIB cases have been observed across the clinical development programme, including the Phase 1 trials, base period and extension period (cut-off 27th May 2017). Although in the reviews that were undertaken to date a causal association of SIB with the tildrakizumab use has not been demonstrated, SIB events have been observed with other mAbs used for psoriasis and most recently in relation with brodalumab (anti-IL-17). Therefore, it has been included as an important potential risk in the RMP and it will be closely monitored and further assessed in on-going studies and in the post-marketing setting. The impact on the risk benefit balance of the product is considered to be low and is expected to remain low in the post-marketing setting.

7. Public health impact:

No impact on public health is expected.

Important Potential Risk: Inflammatory Bowel Disease (IBD)

1. Potential mechanisms:

Unknown, the following published information discuss the relationship between IBD, psoriasis and IL-23.

IBD is considered a potential co-morbidity in patients with psoriasis. Patients with Crohn's Disease (CD) have a 7-times higher risk of developing psoriasis, and psoriasis patients have a 2.9-times higher risk of developing CD, when compared with the general population (Gulliver, 2008, Christophers, 2001).

There is evidence that T-helper cells of type 1 (Th1) and type 17 (Th17) and regulatory T-cells (T-regs) and the consequent cytokine pathway mediated by these cell populations [such as TNFα, interleukin (IL)-1, IL-12/23 and IL-6] act at a systemic level, and can affect the intestine and the joints, metabolic pathways and the cardiovascular system (Grozdev, 2014).

Maxwell et al, using a mouse model of IBD, showed that IL-17 inhibition weakens the intestinal epithelial barrier function and increases inflammation whereas IL-23 inhibition enhances regulatory T cell accumulation, thereby dampening inflammation. Authors concluded that even though IL-17 inhibitors are not efficacious in Crohn's disease, inhibition of IL-23 could be a promising therapeutic approach for (Maxwell, 2015).

2. Evidence source(s) and strength of evidence:

The classification of IBD as a potential risk is based on the safety profile described for other mAbs used for Psoriasis that act on the same pathway but different receptor.

3. Characterisation of risk:

Frequency:

One isolated case of Crohn disease has been reported in the whole clinical development program including the extension studies with a data cut-off 27th May 2017.

Seriousness/outcomes during base period:

The case of Crohn's disease was reported as non-serious and not related by the investigator. The outcome is not recovered/not recovered.

4. Risk factors and risk groups:

Patients with Crohn's Disease (CD) have a 7-times higher risk of developing psoriasis, and psoriasis patients have a 2.9-times higher risk of developing CD, when compared with the general population (Gulliver, 2008; Christopher, 2001, Vlachos, 2016).

5. Preventability:

Given that there is no current evidence of causality of any of IBD events with tildrakizumab treatment, no risk minimisation measures are currently proposed in the product SmPC/PIL. IBD events will be closely monitored in the post-marketing setting and the need for specific risk minimisation measures in the product information will be periodically assessed in the post-marketing setting.

6. Impact on the risk-benefit balance of the product:

One isolated case of IBD has been observed across the clinical development programme, including the Phase 1 trials, base period and extension period (cut-off 27th May 2017). Although in the reviews that were undertaken to date a causal association of IBD with the tildrakizumab use has not been demonstrated, IBD events have been observed with other mAbs used for psoriasis of a different MoA (anti-IL-17). Therefore, it has been included as an important potential risk in the RMP and it will be closely monitored and further assessed in on-going studies and in the post-marketing setting as per regulatory request. The impact on the risk benefit balance of the product is considered to be low and is expected to remain low in the post-marketing setting.

7. Public health impact:

No impact on public health is expected.

SVII.3.2. Presentation of the missing information

- Missing information 1: Safety in pregnant and lactating women

Evidence source

Female patients who were pregnant or lactating were excluded from enrolment in clinical trials. There was a total of 14 pregnancies across the whole clinical development programme. Whilst use in pregnancy is not considered an absolute contraindication in the SmPC, Sec. 4.6 states that "as a precautionary measure it is preferable to avoid use during pregnancy" as there is limited data on use in pregnant women. Given the low numbers of pregnant/lactating women that have been exposed during clinical development, this is a population that requires further characterisation.

Population in need of further characterisation

Use in pregnancy/lactation is considered as requiring further characterisation due to the low numbers of patients exposed in the clinical development programme. It is not anticipated that safety will be different in this population. Use in this population will be further characterised post-authorisation by routine and additional pharmacovigilance activities, via specific ADR follow-up forms and from the information obtained from the planned Post-Authorisation studies.

- Missing information 2: Long-term safety

Evidence source

During the base period of the clinical development programme, patients were exposed for up to 64 weeks. Long-term extension studies are ongoing, which will provide data for up to 4 years. In addition, a registry-based long-term study is planned in order to follow-up patients and provide long-term safety data.

Population in need of further characterisation

Long-term safety is considered as missing information requiring further characterisation as there is currently limited data on long-term safety available from the clinical development programme (up to 64 weeks) and long-term extension studies (up to 4 years). It is not anticipated that the long-term safety profile will be different to that observed so far in the clinical development programme. Long-term safety will be further characterised post-authorisation by routine pharmacovigilance activities and via the registry-based study.

- Missing information 3: Use after recent vaccination with live bacterial or live viral vaccines

Evidence source

Use after recent vaccination with live bacterial or live viral vaccines was a contraindication in the clinical development programme; hence no data is available in this population. Whilst use in this population is not contraindicated in the SmPC, Sec. 4.4 states that treatment should be withheld for 4 weeks following live viral or bacterial vaccination, whilst Sec. 4.5 states that no information is available regarding response to live/inactivated vaccines. Given the

immunomodulatory nature of this product, use after recent vaccination with live vaccines is considered as missing information.

Population in need of further characterisation

Use after recent vaccination with live bacterial or live viral vaccines was a contraindication in the clinical trial programme, hence no data is available in this population. Use after recent vaccination with live vaccines is considered as missing information, due to the immunomodulatory nature of this product. Use in this population will be further characterised post-authorisation by routine pharmacovigilance activities.

- Missing information 4: Use in immunosuppressed patients

Evidence source

Only 8 patients who were immunocompromised based on their history of concomitant drug use were included in the clinical development programme. Given the immunomodulatory nature of this product, use in immunocompromised patients is considered as missing information.

Population in need of further characterisation

Very few patients who were immunocompromised were included in the clinical development programme. Use in this population is considered as missing information due to the immunomodulatory nature of this product. Use in this population will be further characterised post-authorisation by routine pharmacovigilance activities.

- Missing information 5: Use in patients with severe hepatic impairment

Evidence source

No formal trials with tildrakizumab on patients with hepatic impairment have been conducted and patients with significant organ dysfunction (such as significant hepatic dysfunction) were excluded from the clinical trials. Among subjects receiving tildrakizumab during the base period, there were 90 patients with medical history of hepatic impairment in the Phase 2b/3 trials (Source: Statistical Report supporting the Risk Management Plan (RMP)- Table 4). As the product is not contraindicated in this population use in patients with severe hepatic impairment is considered as missing information.

Population in need of further characterisation

No formal trials with tildrakizumab on patients with hepatic impairment have been conducted and patients with significant organ dysfunction (such as significant hepatic dysfunction) were excluded from the clinical trials. Use in patients with severe hepatic impairment is considered as missing information and will be further characterised post-authorisation by routine pharmacovigilance activities.

- Missing information 6: Use in patients with severe renal impairment

Evidence source

No formal trials with tildrakizumab on patients with renal impairment have been conducted and patients with significant organ dysfunction (such as significant renal dysfunction) were excluded from the clinical trials. Pooled data from clinical development studies P003, P010 and P011 shows that when the renal function is assessed based on the Glomerular Filtration Renal estimation (eGFR) at baseline, there were 1328 patients with normal renal function, 609 patients with mild renal impairment, 56 patients with moderate renal impairment and 1 patient with severe renal impairment. There were no patients with renal failure (Source: Statistical Report supporting the Risk Management Plan (RMP)-Table 4_1). As the product is not contraindicated in this population, use in patients with severe renal impairment is considered as missing information.

Population in need of further characterisation

No formal trials with tildrakizumab on patients with renal impairment have been conducted and patients with significant organ dysfunction (such as significant renal dysfunction) were excluded from the clinical trials. Use in patients with severe renal impairment is considered as missing information and will be further characterised post-authorisation by routine pharmacovigilance activities.

Part II: Module SVIII - Summary of the safety concerns

Table 21. Part II: Module SVIII: Summary of safety concerns for tildrakizumab

Important identified risks	**None**
Important potential risks	Hypersensitivity Serious infections Malignancies Major adverse cardiac events Suicidal ideation behaviour (SIB) Inflammatory Bowel Disease (IBD)
Missing information	Safety in pregnant and lactating women Long-term safety Use after recent vaccination with live bacterial or live viral vaccines Use in immunosuppressed patients Use in patients with severe hepatic impairment Use in patients with severe renal impairment

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

III.1 Routine pharmacovigilance activities

As part of the routine pharmacovigilance activities, specific adverse drug reaction (ADR) follow-up questionnaires for: Major Cardiovascular Events, serious infections, malignancies and Suicidal Ideation Behaviour have been developed to monitor these safety concerns. A specific follow-up form for pregnancy has also been developed.

The forms are provided in Annex 4 of the RMP.

Other forms of routine pharmacovigilance activities:

None.

III.2 Additional pharmacovigilance activities

The Applicant plans to perform the following additional pharmacovigilance activities:

- Two Long-Term Safety Extension Studies from both Phase 3 (P010 and P011) clinical trials;
- Tildrakizumab Post-Authorisation Safety Study (PASS) in European Psoriasis Registries;
- An observational study (3357-4) and pregnancy safety related studies 3357-2 and 3357-3 in the US.

The main safety concerns to be addressed with these studies will be malignancies, MACEs, serious infections, SIB, the long-term (> 52 weeks) safety profile of tildrakizumab as well as the safety profile of tildrakizumab in pregnant women. In case it is not feasible to conduct the analysis of pregnancy outcomes, a stand-alone study will be conducted.

A summary of these studies is provided below:

Long-term safety extension studies from Phase 3 clinical trials (P010 and P011)

Study short name and title:

- P010 study: A 64-Week, Phase 3, Randomized, Placebo-Controlled, Parallel Design Study to Evaluate the Efficacy and Safety/Tolerability of Subcutaneous Tildrakizumab (SCH 900222/MK-3222), followed by an Optional Long-Term Safety Extension Study, in Subjects With Moderate-to-Severe Chronic Plaque Psoriasis
- P011 study: A 52-Week, Phase 3, Randomized, Active Comparator and Placebo-Controlled, Parallel Design Study to Evaluate the Efficacy and Safety/Tolerability of Subcutaneous Tildrakizumab (SCH 900222/MK-3222), followed by an Optional Long-Term Safety Extension Study, in Subjects With Moderate-to–Severe Chronic Plaque Psoriasis

Rationale and study objectives:

To assess the long-term safety profile and tolerability of tildrakizumab for up to 4 years.

Study design:

Long-term extension clinical trials in which the patients receive 100 mg or 200 mg of tildrakizumab.

Study population:

Adult subjects (≥18 years of age) with a diagnosis of moderate-to-severe chronic plaque psoriasis (defined as body surface area [BSA] involvement ≥10%, Physician's Global Assessment [PGA] score ≥3, and Psoriasis Area and Severity Index [PASI] score ≥12 at baseline).

Study results summary:

For both P010 and P011, no meaningful differences were observed in the AE rates between participants treated with tildrakizumab 200 mg and those treated with tildrakizumab 100 mg. An overall summary of AEs reported during the extension study is provided by treatment group in Tables 22 and 23.

Table 22. Part III: Adverse Events Summary (All Subjects Treated) - Extension Study P010

	MK-3222 100 mg		MK-3222 200 mg		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population[†]	239		267		506	
with one or more adverse events	216	(90.4)	231	(86.5)	447	(88.3)
with no adverse events	23	(9.6)	36	(13.5)	59	(11.7)
with drug-related[‡] adverse events	44	(18.4)	50	(18.7)	94	(18.6)
with serious adverse events	60	(25.1)	58	(21.7)	118	(23.3)
with serious drug-related[‡] adverse events	12	(5.0)	7	(2.6)	19	(3.8)
who died	3	(1.3)	2	(0.7)	5	(1.0)
discontinued[§] due to an adverse event	26	(10.9)	13	(4.9)	39	(7.7)
discontinued[§] due to a drug-related[‡] adverse event	9	(3.8)	2	(0.7)	11	(2.2)
discontinued[§] due to a serious adverse event	23	(9.6)	7	(2.6)	30	(5.9)
discontinued[§] due to a serious drug-related[‡] adverse event	7	(2.9)	1	(0.4)	8	(1.6)

[†]Subjects who received at least one dose of extension study medication based on the treatment actually received.
[‡]Determined by the investigator to be related to the drug.
[§]Study medication withdrawn.

Table 23. Part III: Adverse Events Summary (All Subjects Treated) - Extension Study P011

	MK-3222 100 mg		MK-3222 200 mg		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population[†]	381		349		730	
with one or more adverse events	321	(84.3)	307	(88.0)	628	(86.0)
with no adverse events	60	(15.7)	42	(12.0)	102	(14.0)
with drug-related[‡] adverse events	91	(23.9)	99	(28.4)	190	(26.0)
with serious adverse events	87	(22.8)	79	(22.6)	166	(22.7)
with serious drug-related[‡] adverse events	8	(2.1)	6	(1.7)	14	(1.9)

	MK-3222 100 mg		MK-3222 200 mg		Total	
	n	(%)	n	(%)	n	(%)
who died	4	(1.0)	2	(0.6)	6	(0.8)
discontinued§ due to an adverse event	16	(4.2)	13	(3.7)	29	(4.0)
discontinued§ due to a drug-related‡ adverse event	4	(1.0)	3	(0.9)	7	(1.0)
discontinued§ due to a serious adverse event	7	(1.8)	8	(2.3)	15	(2.1)
discontinued§ due to a serious drug-related‡ adverse event	1	(0.3)	1	(0.3)	2	(0.3)

† Subjects who received at least one dose of extension study medication based on the treatment actually received.
‡ Determined by the investigator to be related to the drug.
§ Study medication withdrawn.

The most common AEs (≥10% of participants in either P010 or P011) were nasopharyngitis, upper respiratory tract infection, hypertension, and arthralgia, and among these only nasopharyngitis was considered related to the study drug for ≥10% of participants by the Investigator. The incidence rate of serious drug-related AEs was low overall in the extension studies. One or more SAE was reported in 22.7% to 23.3% of participants. Treatment discontinuation due to one or more AE was observed for 7.7% of participants in P010 and 4.0% of participants in P011 during the extension period.

One or more AE led to treatment discontinuation for 39 (7.7%) participants in P010 and 29 (4.0%) participants in P011 over the course of the extension periods. The cumulative 5-year exposure-adjusted incidence of AEs leading to treatment discontinuation was similar to the exposure-adjusted incidence observed during the first year of treatment for both P010 (0.9 to 2.1% vs. 0.3% to 1.0%) and P011 (0.2% vs. 1.4% to 2.6%), suggesting that the incidence of AEs leading to treatment discontinuation did not increase with continued treatment.

Over the course of the long-term extensions, 5 (1.0%) participants in P010 and 6 (0.8%) participants in P011 had one or more SAE with a fatal outcome. Among these, 2 participants in P010 presented events that were considered related to the study drug by the Investigator, both with significant associated risk factors. The only fatal SAE reported by more than 1 participant was completed suicide, which occurred in 1 participant in P010 and 2 participants in P011. All 3 suicides were considered not related to the study drug by the Investigator and important contributing factors were identified in all these cases.

The cumulative 5-year exposure-adjusted incidence of SAEs was similar to the exposure-adjusted incidence observed during the first year of treatment for both P010 (4.4% to 5.2% vs. 5.1% to 8.4%) and P011 (5.6% vs. 6.2% to 6.6%), which suggests that the incidence of SAEs did not increase with continued treatment.

For both P010 and P011, 100 mg and 200 mg, exposure adjusted incidence of severe infections, malignancies, MACEs, and hypersensitivity was similar at Year 1 and cumulatively at Year 5, as follows:

Table 24 . Part III: Exposure-Adjusted Incidence of AESIs at Year 1 and Cumulative 5-Year (ASaT Population)

Parameter	P010				P011			
	Year 1[a]		5-year Cumulative		Year 1[b]		5-year Cumulative	
	100 mg	200 mg	100 mg	200 mg	100 mg	200 mg	100 mg	200 mg
Participants (patient-weeks)	383 (20268)	399 (21795)	256 (65976)	267 (788168)	487 (23763)	527 (21780)	398 (91976)	454 (85396)
AESI, n (Adj)[c]								
Severe infection[d]	4 (1.0)	6 (1.4)	13 (1.0)	19 (1.3)	5 (1.1)	8 (1.9)	16 (0.9)	15 (0.9)
Malignancies[e]	5 (1.3)	6 (1.4)	21 (1.7)	12 (0.8)	8 (1.8)	4 (1.0)	11 (0.6)	15 (0.9)
Nonmelanoma skin cancer	5 (1.3)	4 (1.0)	3 (0.2)	3 (0.2)	4 (0.9)	3 (0.7)	6 (0.3)	6 (0.4)
Melanoma skin cancer	0	0	1 (0.1)	1 (0.1)	1 (0.2)	0	1 (0.1)	2 (0.1)
Extended MACE[f]	1 (0.3)	5 (1.2)	6 (0.5)	9 (0.6)	2 (0.4)	1 (0.2)	7 (0.4)	9 (0.5)
Drug-related hypersensitivity	1 (0.3)	1 (0.2)	2 (0.2)	1 (0.1)	4 (0.9)	1 (0.2)	3 (0.2)	3 (0.2)

Abbreviations: Adj=exposure-adjusted incidence %; ASaT: All Subjects as Treated; AESI: Adverse Event of Special Interest; MACE=major adverse cardiovascular event

a Week 0 to 64. Includes subjects who took at least one dose of Part 1 or Part 2 or Part 3 study medication based on the treatment actually received. Events were counted in each treatment group based on the treatment the subject actually received when the event occurred.

b Week 0 to 52. Includes subjects who took at least one dose of Part 1 or Part 2 or Part 3 study medication based on the treatment actually received. Events were counted in each treatment group based on the treatment the subject actually received. Refer to

c Exposure adjustment is calculated as (52.17857143 weeks * n/person-weeks) *100, where person-weeks = start of treatment to end of treatment.

d Defined as infection meeting the regulatory definition of a serious adverse event, or any infection requiring IV antibiotics whether or not reported as a serious adverse event, as per the regulatory definition.

e Excluding carcinoma in situ of the cervix.

f Includes non-fatal myocardial infarction, non-fatal stroke, unstable angina, coronary revascularization, resuscitated cardiac arrest, and CV deaths that are confirmed as "cardiovascular" or "sudden".

Sources: P010 CSR Table 14.3.8; P011 CSR Table 14.3.8

During the double-blind period, the incidence of these AESIs was similar between placebo and tildrakizumab-treated participants. There is no suggestion of an increase in AESIs occurrence with long-term treatment. The cumulative 5-year exposure-adjusted incidence of AESIs was low and consistent with the exposure-adjusted rates observed in the tildrakizumab-treated participants during the first year of treatment.

It was concluded that tildrakizumab was safe and well tolerated at both 100 mg and 200 mg for a long-term administration and there were no new safety signals observed during the long-term extension studies. The long-term safety profile of tildrakizumab was consistent with that observed during the double-blind period, with no new safety concerns identified.

For more details see: Final Study Report long term extension P10 and long-term extension P11 and Module 2.5 Addendum Clinical Overview. For more details see: Final Study Report long term extension P010 and long-term extension P011 and Module 2.5 Addendum Clinical Overview.

Tildrakizumab PASS Study in European Psoriasis Registries

Study short name and title:

Tildrakizumab Post-Authorisation Safety Study in European Psoriasis Registries (M-14745-40).

Rationale and study objectives:

This observational cohort study aims to assess the long-term safety of tildrakizumab compared to other biological and non-biological therapies used in the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy in a real-world clinical setting; and so to address whether the use of tildrakizumab is associated with an increased risk of events of special interest for biologic therapies for psoriasis.

The specific primary objectives are the following: To evaluate the risk of malignancies, MACEs, serious infections, hypersensitivity, IBD and SIB in patients receiving tildrakizumab compared to patient who receive other biologics or non-biologic systemic therapies for psoriasis.

The secondary objectives are the following: To evaluate the incidence of all AEs and SAEs, and to collect safety data of pregnant and lactating female patients with psoriasis treated with tildrakizumab. Pregnancy outcomes of interest are as follows: major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes. Additionally, infant outcomes including neonatal deaths, infections in the first 6 months of life, and effects on postnatal growth and development, through the first year of life.

Study design:

The study is a long-term, non-interventional, observational post-authorisation safety study. The study will use a prospective cohort design and data primarily collected in established registers of patients with psoriasis treated with systemic therapies in European countries. Data from the registers will be used to identify cohorts of patients with psoriasis who are users of tildrakizumab, other biologics or non-biologic systemic therapies. Patients will be followed from cohort entry for up to 8 years to determine the incidence of the safety concerns of interest.

Study population:

Adult patients (18 years of age or older) diagnosed with psoriasis who are treated with any biologic or non-biological systemic therapy.

Milestones:

- Final study protocol to be submitted to PRAC within 3 months of the EC decision. (Submitted to EMA in January 2019)
- Start of data collection: Q3/2020
- End of data collection: Q2/2028
- Final report of study results: Q2/2029

Observational Study to assess long-term safety 3357-4 (TILD-19-01) (in US)

Study short name and title:

Prospective, observational study to assess the long-term safety of tildrakizumab compared with other therapies used in the treatment of adults with moderate to severe psoriasis in the course of routine clinical care.

Rationale and study objectives:

This observational study aims to assess the long-term safety of tildrakizumab compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in the course of actual clinical care.

The study's primary outcome is the long-term risk of malignancy. Secondary outcomes include, but are not limited to, serious infections, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal and hematologic adverse events. Patients shall be enrolled over an initial 4-year period and follow for a minimum of 8 years from the time of enrolment.

Milestones (subject to the commercialization in the US):

Final protocol Submission: Feb 2020. (Submitted to FDA on 27 Sep 2019)

Study completion: Feb 2033

Final report submission: Feb 2034

Observational pregnancy safety related study 3357-2 (in US)

Study short name and title:

Observational surveillance study to assess the maternal, foetal and infant outcomes of women exposed to tildrakizumab compared to other therapies used in the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy in the course of clinical care.

Rationale and study objectives:

The primary objective of the study is to assess the incidence of major congenital malformations, spontaneous abortions, stillbirths, elective terminations and small for gestational age and other adverse pregnancy outcomes in pregnant women exposed to tildrakizumab in the course of routine clinical care compared to an unexposed control population of psoriasis patients that are exposed to other biologics approved for treatment of psoriasis.

The secondary objectives of the study are to assess the incidence of infant outcomes including neonatal deaths, infections in first 6 months of life and effects on postnatal growth and development through first year of life.

Study design:

The study is a prospective observational cohort design using data collected from this prospective, multicentre, observational registry for adult subjects with psoriasis.

Study population:

It is expected that approximately 250 adult female patients (18 years of age or older) diagnosed with plaque psoriasis by a dermatologist who have started on or switched to an FDA-approved biologic for the treatment of psoriasis and have pregnancy and reported confirmed or suspected maternal exposure to tildrakizumab or other biologics any time during pregnancy or shortly before pregnancy (up to 8 weeks before LMP) will be included.

The study population will comprise all patients within the registry, including those who receive tildrakizumab following approval and marketing, and those receiving other biologics approved for psoriasis. For the primary and secondary objectives, an age -matched primary comparator population will be assembled from the registry population consisting of pregnant women with moderate-to-severe psoriasis exposed to other biologic medications approved to treat psoriasis.

Milestones (subject to commercialization in the US):

Final protocol Submission: Jun 2019. (Submitted to FDA on 28 June 2019)

Study completion: Jan 2029

Final report submission: Jan 2030

Retrospective pregnancy safety related study 3357-3 (in US)

Study short name and title:

Retrospective cohort study to assess the association between some maternal, foetal and infant outcomes with exposure to tildrakizumab compared to the population unexposed to tildrakizumab i.e., receiving other therapies used in the treatment of adults with moderate to severe plaque psoriasis.

Rationale and study objectives:

The primary objective of the study is to evaluate the association of tildrakizumab exposure with major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths and infant infections compared to other biologic therapies used in the treatment of adults with moderate to severe plaque psoriasis.

Study design:

The primary objective of the study is to evaluate the association of tildrakizumab exposure with major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths and infant infections compared to other biologic therapies used in the treatment of adults with moderate to severe plaque psoriasis.

Study population:

Database of female psoriasis patients from claims records or electronic medical records or other registries like the Prospective Pregnancy Registry will be used to identify patients. The long-term safety registry will be examined on an ongoing basis to detect cases with pre-specified outcome definitions.

It is expected that approximately 250 adult female patients (18 years of age or older) diagnosed with psoriasis by a dermatologist who have a history of treatment with tildrakizumab or an FDA-approved biologic for the treatment of psoriasis during pregnancy or shortly before pregnancy (up to 8 weeks before LMP) will be included.

Milestones (subject to the commercialization in the US):

Final protocol Submission: Aug 2019. (Protocol Submitted to FDA on 28 June 2019)

Study completion: Jan 2026

Final report submission: Jan 2027

III.3 Summary Table of additional Pharmacovigilance activities

Table 25. Part III: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Long-term safety extension period (up to 4 years) study from study P010 Study Completed	To assess the long-term safety profile and tolerability of tildrakizumab for up to 4 years. The study will also monitor the tier 1 adverse events which include MACEs, serious infections, malignancies, hypersensitivity reactions and injection site reactions.	Long-term safety profile of tildrakizumab	Annual update	Within PSUR
			Final report	Completed in September 2023)
			Final report submission to EMA	Q4 2023
Long-term safety extension period (up to 4 years) study from study P011 Study Completed	To assess the long-term safety profile and tolerability of tildrakizumab for up to 4 years. The study will also monitor the tier 1 adverse events which include MACEs, serious infections, malignancies, hypersensitivity reactions and injection site reactions.	Long-term safety profile of tildrakizumab	Annual update	Within PSUR
			Final report	Completed on September 2023
			Final report submission to EMA	Q4 2023
Tildrakizumab Post-Authorisation Safety Study (PASS) in European Psoriasis Registry (M-14745-40) On-going	To collect long-term safety data in particular relating to event of special interest (important potential risks and pregnancy related outcomes) for tildrakizumab. To further characterize the long-term safety profile of tildrakizumab in the treatment of psoriasis under conditions of routine clinical care.	Malignancies MACEs Serious infections SIBH Hypersensitivity IBD Safety in pregnant and lactating women	Submission protocol for evaluation	Submitted in January 2019
			Annual update	Annual progress report
			Final report	Q2 2029

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Pregnancy safety related study 3357-2 (US) On-going	To assess the incidence of major congenital malformations, spontaneous abortions, stillbirths, elective terminations and small for gestational age and other adverse pregnancy outcomes in pregnant women exposed to tildrakizumab	Congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, neonatal deaths and infant infections	Annual update	Within PSUR
			Final report	Jan 2030
Pregnancy safety related study 3357-3 (US) Ongoing	To evaluate the association of tildrakizumab exposure with major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths and infant infections	Congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths and infant infections	Annual update	Within PSUR
			Final report	Jan 2027
Tildrakizumab Post authorization observational study (US) 3357-4 On-going	To further characterize the long-term safety profile of tildrakizumab in the treatment of psoriasis under conditions of routine clinical care. To collect long-term safety data in particular relating to important potential risks for tildrakizumab.	Malignancies Serious Infections MACEs	Annual update	Within PSUR
			Final Report	Feb 2034

Part IV: Plans for post-authorisation efficacy studies

Based on the data presented and discussed in RMP Part II modules SIII on clinical trial exposure and SIV on populations not studied in clinical trials, there are no studies considered necessary to further investigate the efficacy of tildrakizumab in the proposed therapeutic indication "treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy".

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 26. Part V: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimisation activities
Hypersensitivity	**Routine risk communication:** • SmPC Sec. 4.3 • PL Sec. 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendation of discontinuing treatment if a serious hypersensitivity reaction occurs in SmPC Sec. 4.4. • How to detect early signs and symptoms of hypersensitivity reactions and recommendation of when stop treatment or seek medical help in PL Sec. 2 and Sec. 4. **Other routine risk minimisation measures beyond the Product Information:** • Pack sizes: There are two pack sizes, one for the recommended dose of 100 mg containing 1 pre-filled syringe of 100 mg/mL, and a second pack size for the 200 mg recommended dose, a pack containing two pre-filled syringe of 100 mg/mL • Prescription only medicine
Serious infections	**Routine risk communication:** • SmPC Sec. 4.4 • PL Sec. 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC Sec. 4.3 contraindicates the use of Ilumetri in patients with clinically important active infection (e.g., active tuberculosis) • Recommendations for HCPs to be cautious when consider the use of Ilumetri in patients with a chronic infection or a history of recurrent or recent serious infection is given in Sec. 4.4 of SmPC. Additionally, the SmPC recommends HCPs to instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur and recommends close monitoring for patient who develops a serious infection, and do not administer Ilumetri until the infection resolves. • PL Sec. 2 reflects when Ilumetri should not be used. Additionally, recommendation for patients to talk with their doctor, pharmacist or nurse before using Ilumetri to tell them if they currently have an infection or if they

	have long-term or repeated infections is given in Sec. 2 of PL. When stop treatment or seek medical help is also warned in Sec. 2 of PL **Other routine risk minimisation measures beyond the Product Information:** • Pack size: There are two pack sizes, one for the recommended dose of 100 mg containing 1 pre-filled syringe of 100 mg/mL, and a second pack size for the 200 mg recommended dose, a pack containing two pre-filled syringe of 100 mg/mL • Prescription only medicine
Malignancies	**Routine risk communication:** • Sec. 5.3 Preclinical safety data **Other routine risk minimisation measures beyond the Product Information:** • Pack size: each pack contains two pre-filled syringe contains 100 mg of tildrakizumab in 1 ml • Prescription only medicine
Major adverse cardiovascular events (MACE)	**Routine risk communication:** • None proposed at present. No increased risk of MACE was observed in the clinical development programme **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • None proposed at present. No increased risk of MACE was observed in the clinical development programme **Other routine risk minimisation measures beyond the Product Information:** • Pack size: There are two pack sizes, one for the recommended dose of 100 mg containing 1 pre-filled syringe of 100 mg/mL, and a second pack size for the 200 mg recommended dose, a pack containing two pre-filled syringe of 100 mg/mL • Prescription only medicine
Suicidal ideation behaviour (SIB)	**Routine risk communication:** • None proposed at present. No increased risk of SIB was observed in the clinical development programme **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • None proposed at present. No increased risk of SIB was observed in the clinical development programme **Other routine risk minimisation measures beyond the Product Information:** • Pack size: There are two pack sizes, one for the recommended dose of 100 mg containing 1 pre-filled syringe of 100 mg/mL, and a second pack size for the 200 mg recommended dose, a pack containing two pre-filled syringe of 100 mg/mL • Prescription only medicine
Inflammatory Bowel Disease (IBD)	**Routine risk communication:** • None proposed at present. No increased risk of IBD was observed in the clinical development programme **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • None proposed at present. No increased risk of IBD was observed in the clinical development programme **Other routine risk minimisation measures beyond the Product Information:** • Pack size: There are two pack sizes, one for the recommended dose of 100 mg containing 1 pre-filled syringe of 100 mg/mL, and a second pack size for the 200 mg recommended dose, a pack containing two pre-filled syringe of 100 mg/mL • Prescription only medicine

Missing information

Safety concern	Routine risk minimisation activities
Safety in pregnant and lactating women	**Routine risk communication:** • Sec. 4.6 Fertility, pregnancy and lactation • Sec. 5.3 Preclinical safety data **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendation for potential childbearing, pregnant and breast-feeding women is provided in Sec. 4.6 of SmPC. • Recommendation for potential childbearing, pregnant and breast-feeding women is provided is also provided in Sec. 2 of PL **Other routine risk minimisation measures beyond the Product Information:** • Pack size: each pack contains two pre-filled syringe contains 100 mg of tildrakizumab in 1 ml • Prescription only medicine
Long-term safety profile	**Routine risk communication:** • None proposed at present. No increased risk with the long-term use was observed in the clinical development programme **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • None proposed at present. No increased risk with the long-term use was observed in the clinical development programme **Other routine risk minimisation measures beyond the Product Information:** • Pack size: There are two pack sizes, one for the recommended dose of 100 mg containing 1 pre-filled syringe of 100 mg/mL, and a second pack size for the 200 mg recommended dose, a pack containing two pre-filled syringe of 100 mg/mL • Prescription only medicine
Use after recent vaccination with live bacterial or live viral vaccines	**Routine risk communication:** • SmPC Sec. 4.4 and 4.5 • PL Sec. 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendations about vaccinations prior to initiating treatment and regarding to when live vaccines should not be given concurrently with Ilumetri is provided in Sec. 4.4 and 4.5 of SmPC. • Recommendation for patients to talk with their doctor, pharmacist or nurse before using Ilumetri regarding the patient vaccination status and when live vaccines should not be given is provided in PL Sec. 2 **Other routine risk minimisation measures beyond the Product Information:** • Pack size: There are two pack sizes, one for the recommended dose of 100 mg containing 1 pre-filled syringe of 100 mg/mL, and a second pack size for the 200 mg recommended dose, a pack containing two pre-filled syringe of 100 mg/mL • Prescription only medicine

Safety concern	Routine risk minimisation activities
Use in immunosuppressed patients	**Routine risk communication:** • SmPC Sec. 4.5 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendation for patients to tell their doctor, pharmacist or nurse if they are taken any immunosuppressant is given in PL Sec. 2 **Other routine risk minimisation measures beyond the Product Information:** • Pack size: There are two pack sizes, one for the recommended dose of 100 mg containing 1 pre-filled syringe of 100 mg/mL, and a second pack size for the 200 mg recommended dose, a pack containing two pre-filled syringe of 100 mg/mL • Prescription only medicine
Use in patients with severe hepatic impairment	**Routine risk communication:** • SmPC Sec. 4.2 and Sec 5.2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimisation measures beyond the Product Information:** • Pack size: There are two pack sizes, one for the recommended dose of 100 mg containing 1 pre-filled syringe of 100 mg/mL, and a second pack size for the 200 mg recommended dose, a pack containing two pre-filled syringe of 100 mg/mL • Prescription only medicine
Use in patients with severe renal impairment	**Routine risk communication:** • SmPC Sec. 4.2 and Sec 5.2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimisation measures beyond the Product Information:** • Pack size: There are two pack sizes, one for the recommended dose of 100 mg containing 1 pre-filled syringe of 100 mg/mL, and a second pack size for the 200 mg recommended dose, a pack containing two pre-filled syringe of 100 mg/mL • Prescription only medicine

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 27. Part V: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hypersensitivity	**Routine risk minimisation** • SmPC Sec. 4.3 • PL Sec. 2 • Prescription only medicine	**Additional PV** • Review of safety data from long-term (4 years) extension studies • Monitoring of Hypersensitivity in PASS in European Psoriasis Registries(M-14745-40)
Serious infections	**Routine risk minimisation** • SmPC Sec. 4.3 and Sec. 4.4 • PL Sec. 2 • Prescription only medicine	**Routine PV** • Specific ADR follow-up form **Additional PV** • Review of safety data from long-term (4 years) extension studies • Monitoring of serious infections in PASS in European Psoriasis Registries(M-14745-40) • Monitoring of serious infections in US observational Study 3357-4
Malignancies	**Routine risk minimisation** • SmPC Sec. 5.3 • Prescription only medicine	**Routine PV** • Specific ADR follow-up form for malignancies. **Additional PV** • Review of safety data from long-term (4 years) extension studies. • Monitoring of malignancies in PASS in European Psoriasis Registries (M-14745-40) • Monitoring of Malignancies in US observational Study 3357-4
Major adverse cardiovascular events (MACE)	**Routine risk minimisation** • None proposed in product information as no increased risk of MACE was observed in clinical development. • Prescription only medicine	**Routine PV** • Specific ADR follow-up form for MACE. **Additional PV** • Review of safety data from long-term (4 years) extension studies. • Monitoring of MACEs in PASS in European Psoriasis Registries (M-14745-40) • Monitoring of MACE in US observational Study 3357-4
Suicidal ideation behavior (SIB)	**Routine risk minimisation** • None proposed in product information as no increased risk of SIB was observed in clinical development. • Prescription only medicine	**Routine PV** • Specific ADR follow-up form for SIB. **Additional PV**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		• Review of safety data from long-term (4 years) extension studies. • Monitoring of SIB in PASS in European Psoriasis Registries (M-14745-40)
Safety in pregnant and lactating women	**Routine risk minimisation** • SmPC Sec. 4.6 and Sec. 5.3 • PL Sec. 2 • Prescription only medicine	**Routine PV** • Specific pregnancy follow-up form **Additional PV** • Monitoring in PASS in European psoriasis registries (M-14745-40) • Pregnancy safety related studies 3357-2 and 3357-3 (US)
Inflammatory Bowel Disease (IBD)	**Routine risk minimisation** • None proposed in product information as no increased risk of IBD was observed in clinical development. • Prescription only medicine	**Routine PV** • None specific **Additional PV** • Review of safety data from long-term (4 years) extension studies. • Monitoring of IBD in PASS in European Psoriasis Registries(M-14745-40)
Long-term safety profile	**Routine risk minimisation** • None proposed in product information as no increased risk with long-term use was observed in clinical development. • Prescription only medicine	**Additional PV** • Review of safety data from long-term (4 years) extension studies • PASS in European Psoriasis Registries. (M-14745-40) • US observational Study 3357-4
Use after recent vaccination with live bacterial or live viral vaccines	**Routine risk minimisation** • SmPC Sec. 4.4 and 4.5 • PL Sec. 2 • Prescription only medicine	**Routine PV** • Specific ADR follow-up form for "serious infection" includes questions related with vaccination status
Use in immunosuppressed patients	**Routine risk minimisation** • SmPC Sec. 4.5 • PL Sec. 2 • Prescription only medicine	**Routine PV** • Specific ADR follow-up form for "serious infection" includes questions related with immune system status of the patient and questions related with prior and concomitant immunosuppressant medications
Use in patients with severe hepatic impairment	**Routine risk minimisation** • SmPC Sec. 4.2 and Sec 5.2 • Prescription only medicine	**Routine PV** • Periodic review of safety reports with medical history of hepatic impairment
Use in patients with severe renal impairment	**Routine risk minimisation** • SmPC Sec. 4.2 and Sec 5.2 • Prescription only medicine	**Routine PV** • Periodic review of safety reports with medical history of renal impairment

Part VI: Summary of the risk management plan

Summary of risk management plan for tildrakizumab 100 mg solution for injection in pre-filled syringe (Ilumetri)

This is a summary of the risk management plan (RMP) for Ilumetri 100 mg Solution for injection. The RMP details important risks of Ilumetri, how these risks can be minimised, and how more information will be obtained about Ilumetri's risks and uncertainties (missing information).

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

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

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

I. The medicine and what it is used for

Ilumetri is authorised for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy (see SmPC for the full indication). It contains tildrakizumab as the active substance and it is given by subcutaneous injection.

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

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

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

- 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 sizes — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

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

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

II.A List of important risks and missing information

Important risks of Ilumetri 100 mg Solution for injection 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 Ilumetri. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 28. Part VI: List of important risks and missing information

Important identified risks	None
Important potential risks	Hypersensitivity Serious infections Malignancies Major adverse cardiac events Suicidal ideation behaviour (SIB) Inflammatory Bowel Disease (IBD)
Missing information	Safety in pregnant and lactating women Long-term safety Use after recent vaccination with live bacterial or live viral vaccines Use in immunosuppressed patients Use in patients with severe hepatic impairment Use in patients with severe renal impairment

II.B Summary of important risks

Table 29. Part VI: Important potential risks

Important potential risk: Hypersensitivity	
Evidence for linking the risk to the medicine	Treatment with monoclonal antibodies may lead to the development of serious anaphylactic or anaphylactoid hypersensitivity reactions, therefore hypersensitivity is considered as a potential risk in the RMP. The classification of hypersensitivity as a potential risk is based on evidence from literature the safety profile described for similar mAbs used for Psoriasis and form the tildrakizumab clinical development programme
Risk factors and risk groups	None identified
Risk minimisation measures	Routine risk minimisation measures • SmPC Sec. 4.3 • PL Sec. 2 • Pack size • Prescription only medicine

Additional pharmacovigilance activities	Additional pharmacovigilance activities • Review of safety data from long-term (4 years) extension studies • Post Authorisation Safety Study (PASS) in European Psoriasis Registries See Sec. II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Serious infections	
Evidence for linking the risk to the medicine	The classification of serious infections as a potential risk is based on evidence from the clinical development programme and the safety profile described for similar MABs that acts in the same pathways used for Psoriasis. Animal studies do not suggest that tildrakizumab produces a detrimental effect on the immune system. Tildrakizumab has an immunomodulatory mode of action, therefore serious infection is considered a potential risk in the RMP and will be monitored in the post-marketing setting.
Risk factors and risk groups	Patients with concomitant chronic debilitating conditions (such as haematological or lymphoreticular malignancies, organ transplanted patients, severe stages of rheumatoid arthritis or systemic lupus erythematosus) who require concomitant immunosuppressive therapies such as steroids at immunosuppressive doses, methotrexate, immunosuppressant or tumour necrosis factor α (TNFα) antagonists (Fica, 2014). A recent systemic review showed that there may be a small increased risk of overall infection related to the short-term use of TNFα antagonists in the treatment of psoriasis, the majority of infections were non-serious (97.6%) and were upper respiratory tract infections (Dommasch, 2011). It is well-recognised that serious infections including atypical infections like TB have been reported with the use of TNF-alpha inhibitors in psoriasis (Dommasch, 2011).
Risk minimisation measures	Routine risk minimisation measures • SmPC Sec. 4.3 and 4.4 • PL Sec. 2 • Pack size • Prescription only medicine
Additional pharmacovigilance activities	Additional pharmacovigilance activities • Review of safety data from long-term (4 years) extension studies • PASS in European Psoriasis Registries • US Observational Study See Sec. II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Malignancies	
Evidence for linking the risk to the medicine	The classification of malignancies as a potential risk is based on the safety profile described for similar mAbs that acts in the same pathways used for Psoriasis and evidence from the clinical development programme. Animal studies for tildrakizumab have shown no increase in carcinogenic risk. Tildrakizumab has however an immunomodulatory

	mode of action, therefore malignancies is considered as a potential risk in the RMP and will be further assessed in the post-marketing setting.
Risk factors and risk groups	Cancer risk seems to be higher in patients with severe psoriasis (Beyaert, 2013). Patients with long standing psoriasis seem to be at an increased risk for colon, bladder and kidney cancer (Brauchli, 2009). Patients receiving high dose PUVA and methotrexate for psoriasis are at an increased risk of skin cancer. In a US prospective PUVA follow-up study of patients with severe psoriasis, more than 25% of patients exposed to high doses of PUVA developed squamous cell cancer (SCC): the relative risk of SCC for patients exposed to high dose PUVA was 5.9 (95% CI 4.0-8.7) compared to those exposed to low dose PUVA. High dose methotrexate was determined to be an independent risk factor for developing SCC with a relative risk of 2.1(95% CI 1.4-2.8) compared to low or no exposure to methotrexate (Stern, 1994).
Risk minimisation measures	Routine risk minimisation measures • SmPC Sec. 5.3 • Pack size • Prescription only medicine
Additional pharmacovigilance activities	Additional pharmacovigilance activities • Review of safety data from long-term (4 years) extension studies • PASS in European Psoriasis Registries • US Observational Study See Sec. II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Major adverse cardiac events (MACE)	
Evidence for linking the risk to the medicine	Psoriasis patients have an increased risk of cardiovascular events due to overlapping mechanisms of systemic inflammation; therefore, MACE is considered a potential risk in the RMP and will be further assessed in the post-marketing setting. The classification of MACE as a potential risk is based on evidence from the clinical development programme, the safety profile described for similar mAbs that acts in the same pathways used for Psoriasis.
Risk factors and risk groups	Patients with psoriasis are at increased risk of myocardial infarction (MI) and stroke (Armstrong, 2013) and of MACE (Parisi, 2015) and this risk appears to increase with severity of disease (Armstrong, 2013; Parisi, 2015; Mehta, 2011). The increased cardiovascular risk observed in psoriasis may result from a number of often related risk factors including: smoking, obesity, hypertension and alcohol misuse. In addition, the use of dyslipidaemic therapies, such as corticosteroids, acitretin and ciclosporin and an associated unfavourable lipid profile with high triglycerides and low HDL cholesterol may contribute. Psoriasis itself is an independent risk factor for MACE (Mehta, 2011) and the overall increased risk may be related to a combination of these factors in the patient (Mrowietz, 2006).
Risk minimisation measures	Routine risk minimisation measures • Pack size • Prescription only medicine

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Review of safety data from long-term (4 years) extension studies • PASS in European Psoriasis Registries • US Observational Study See Sec. II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Suicidal ideation behaviour (SIB)	
Evidence for linking the risk to the medicine	The classification of SIB as a potential risk is based on the safety profile described for similar mAbs that acts in the same pathways used for Psoriasis and on evidence from the clinical development programme. Psoriasis patients have an increased risk of depression and suicidal ideation. SIB events have been observed with monoclonal antibodies used in psoriasis, therefore SIB is considered as a potential risk in the RMP and will be closely monitored in the post-marketing setting.
Risk factors and risk groups	Patients with psoriasis have an increased prevalence of the psychiatric disorders anxiety and depressive disorders (30% and 60% respectively). About 10% of psoriasis patients consider the possibility of suicide (Gupta, 1998). Patients with psoriasis are at a higher risk of depression, suicidal ideation, suicide attempt and completed suicide (Gupta, 1998; Kurd, 2010; Koo, 2017).
Risk minimisation measures	Routine risk minimisation measures • Pack size • Prescription only medicine
Additional pharmacovigilance activities	Additional pharmacovigilance activities • Review of safety data from long-term (4 years) extension studies • PASS in European Psoriasis Registries See Sec. II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Inflammatory Bowel Disease (IBD)	
Evidence for linking the risk to the medicine	IBD events have been observed with other monoclonal antibodies (known as IL-17 inhibitors) used in psoriasis, therefore IBD is considered as a potential risk in the RMP and will be closely monitored in the post-marketing setting.
Risk factors and risk groups	IBD is considered a potential co-morbidity in patients with psoriasis. Patients with Crohn's Disease (CD) have a 7-times higher risk of developing psoriasis, and psoriasis patients have a 2.9-times higher risk of developing CD, when compared with the general population (Guliver, 2008; Christophers, 2001; Vlachos, 2016).
Risk minimisation measures	Routine risk minimisation measures • Pack size • Prescription only medicine
Additional pharmacovigilance activities	Additional pharmacovigilance activities • Review of safety data from long-term (4 years) extension studies • PASS in European Psoriasis Registries

	See Sec. II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Safety in pregnant and lactating women	
Risk minimisation measures	Routine risk minimisation measures • SmPC Sec. 4.6 and 5.3 • PL Sec. 2 • Pack size • Prescription only medicine
Additional pharmacovigilance activities	Additional pharmacovigilance activities • Pregnancy safety related studies (US). • PASS in European Psoriasis Registries

Missing information: Long-term safety	
Risk minimisation measures	Routine risk minimisation measures • Pack size • Prescription only medicine
Additional pharmacovigilance activities	Additional pharmacovigilance activities • Review of safety data from long-term (4 years) extension studies • PASS in European Psoriasis Registries • US Observational Study See Sec. II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Use after recent vaccination with live bacterial or live viral vaccines	
Risk minimisation measures	Routine risk minimisation measures • SmPC Sec. 4.4 and 4.5 • PL Sec. 2 • Pack size • Prescription only medicine

Missing information: Use in immunosuppressed patients	
Risk minimisation measures	Routine risk minimisation measures • SmPC Sec. 4.5 • PL Sec. 2 • Pack size • Prescription only medicine

Missing information: Use in patients with severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures • SmPC Sec. 4.2 and Sec 5.2 • Pack size • Prescription only medicine

Missing information: Use in patients with severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures • SmPC Sec. 4.2 and Sec 5.2 • Pack size • Prescription only medicine

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 Ilumetri 100 mg Solution for injection.

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

1. **P010 study:** A 64-Week, Phase 3, Randomized, Placebo-Controlled, Parallel Design Study to Evaluate the Efficacy and Safety/Tolerability of Subcutaneous Tildrakizumab (SCH 900222/MK-3222), Followed by an Optional Long-Term Safety Extension Study, in Subjects With Moderate-to-Severe Chronic Plaque Psoriasis.

   Purpose of the study: To assess the long-term safety profile and tolerability of tildrakizumab for up to 4 years.

2. **P011 study**: A 52-Week, Phase 3, Randomized, Active Comparator and Placebo-Controlled, Parallel Design Study to Evaluate the Efficacy and Safety/Tolerability of Subcutaneous Tildrakizumab (SCH 900222/MK-3222), followed by an Optional Long-Term Safety Extension Study, in Subjects With Moderate-to–Severe Chronic Plaque Psoriasis.

   Purpose of the study: To assess the long-term safety profile and tolerability of tildrakizumab for up to 4 years.

3. **PASS in European Psoriasis Registries (M-14745-40):** An observational cohort study to assess the long-term safety of tildrakizumab compared to other biological therapies used in the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy in a real world clinical setting.

   Purpose of the study: To address whether the use of tildrakizumab is associated with an increased risk of events of special interest (Malignancies, MACEs, serious infections SIB, Hypersensitivity and IBD) for biologic therapies for psoriasis in new users of tildrakizumab compared to “other biologics” and to “non-biologic systemic therapies” as well study pregnancy related outcomes in patients exposed to tildrakizumab.

4. **Tildrakizumab Post-authorization observational study 3357-4 (US):** An observational study to assess the long-term safety of tildrakizumab compared to other therapies used in the treatment of adults with moderate to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in the course of actual clinical care.

   Purpose of the study: To assess the long-term risk of malignancy, serious infections, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal and hematologic adverse events.

5. **Pregnancy safety related study 3357-2:** A prospective observational study to assess the maternal, foetal and infant outcomes of women exposed to tildrakizumab compared to other therapies used in the treatment of adults with moderate to severe plaque psoriasis.

   Purpose of the study: To assess the incidence of major congenital malformations, spontaneous abortions, stillbirths, elective terminations and small for gestational age and other adverse pregnancy outcomes in pregnant women exposed to tildrakizumab in the course of routine clinical care compared to an unexposed control population of psoriasis patients that are exposed to other biologics approved for treatment of psoriasis.

6. **Pregnancy safety related study 3357-3:** A retrospective study 3357-3 to assess the association between some maternal, foetal and infant outcomes with exposure to tildrakizumab compared to the population receiving other therapies used in the treatment of adults with moderate to severe plaque psoriasis.

   Purpose of the study: To evaluate the association of tildrakizumab exposure with major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths and infant infections compared to other biologic therapies used in the treatment of adults with moderate to severe plaque psoriasis.

Part VII: Annexes

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Annex 4: Specific adverse drug reaction follow-up forms

Specific ADR follow-up form for Major Cardiovascular Events (MACEs)
Specific ADR follow-up form for Serious infections
Specific ADR follow-up form for malignancies
Specific ADR follow-up form for Depression and Suicidal Ideation Behavior (SIB)
Specific ADR follow-up form for pregnancy

1. Pharmacological anamnesis

- Which dose of Tildrakizumab was the patient on?
- Which was the time interval from starting Tildrakizumab to the event onset?
- Was there a positive dechallenge?
- Did the patient recover completely? No □ Yes □ Specify:

2. Event (MACE):

<table>
<tr><td colspan="2">• Which was the final diagnosis?</td></tr>
<tr><td colspan="2">• How was the diagnosis made? Specify:</td></tr>
<tr><td>• Had the patient other symptoms?
No □ Yes □</td><td>Specify: (Dyspnoea, dizziness, chest pain, hypotension etc.)</td></tr>
<tr><td colspan="2">• Please provide tests results (Chest X-ray, ECG, Scanner, Eco Doppler and specific blood tests**)</td></tr>
</table>

- Please provide treatment details and summary of **medical report:**

**: Please provide results and date of full blood count, glucose, urea, creatinine, cholesterol (total, LDL, HDL), TG, liver function, ions (Na, K, Mg), CK, coagulation parameters, troponin, LDH, gasometry.

3. Family Medical History:

Sudden death:	No □ Yes □	Any family history of Heart disease:	No □ Yes □
Hypertension:	No □ Yes □	Diabetes:	No □ Yes □

4. Cardiovascular Risk Factors:

• Age:		• Gender:
• Obesity	No □ Yes □	BMI:
• Smoking:	No □ Yes □	Current □ Ex □ Pack-year:
• Diabetes:	No □ Yes □	Years of evolution: Is it well controlled: No □ Yes □
• Dyslipidaemia:	No □ Yes □	Specify:
• Sedentary lifestyle / job:	No □ Yes □	Specify:
• Illicit drug use, i.e.: cocaine, amphetamines	No □ Yes □	Specify:

- Contraceptive use No □ Yes □ Specify:

***Specify:** (when it started, happened, or if it is on-going? Its severity, etc…

5. Medical History, particularly personal history of any of the following:

- QT prolongation: No □ Yes □ Specify*:
- Cardiac arrhythmia: No □ Yes □ Specify*:
- Ischaemic cardiac disease: (MI, Angina, etc.) No □ Yes □ Specify*:
- Cardiac valve disease: No □ Yes □ Specify*:
- Heart failure: No □ Yes □ Specify*:

• Other cardiac disorders: (Pericardial disease, cardiomyopathy, endocarditis)	No □ Yes □	Specify*:
• Previous heart surgery or intervention: (Pacemaker, By pass, CABG, PCI, etc.)	No □ Yes □	Specify*:
• Atherosclerosis or PAD	No □ Yes □	Specify*:
• Aneurysm or aortic dissection:	No □ Yes □	Specify*:
• Coagulation disorder:	No □ Yes □	Specify*:
• History of thrombosis or embolism	No □ Yes □	Specify*:
• Any relevant concomitant disease: (liver, renal, respiratory, immunological, neoplasm, etc.)	No □ Yes □	Specify*:

***Specify**: (when it started, happened, or if it is on-going? Its severity, etc…

6). Concomitant medications (including OTC and herbals):

Was the patient taking any prescribed medication or herbals: No □ Yes □

If yes, specify: (dates of therapy, dosage, indications)_____

Was there any recent change in this medication due to any cause: No □ Yes □

If yes, specify: _____

1. Pharmacological anamnesis

- Which dose of Tildrakizumab was the patient on?

- Which was the time interval from starting Tildrakizumab to the event onset?

- Which was the time interval from the last Tildrakizumab administration and the event onset?

- Specify as much as possible the cumulative Tildrakizumab dose (number of doses) received by the patient-.

- Did the patient recover completely? No □ Yes □ Specify:

2. Event of MALIGNANCY

• What is the **type of malignancy**? (specify the stage if available)
• How was the diagnosis made? Specify: (initial symptoms / date)
• Please provide **test results** (cytology, biopsy, histopathological, images, etc)

- Please provide **treatment** details and **summary of the medical report:**

3. Risk Factors for Malignancies:

• Age:		• Gender:
• Family or personal history of cancer	No □ Yes □	
• Obesity	No □ Yes □	BMI:
• Smoking:	No □ Yes □	Current □ Ex □ Pack-year:
• Alcohol consumption:	No □ Yes □	Current □ Ex □ Drinks/day/type:
• Diabetes:	No □ Yes □	Years of evolution: Controlled: No □ Yes □
• Infections (i.e.: VPH, VHC, Epstein Barr)	No □ Yes □	Specify:
• Other relevant diseases: (liver, renal, GI, respiratory, immunological, etc.)	No □ Yes □	Specify*:

***Specify:** (when it started, happened, or if it is on-going? Its severity, etc…

4. Specific Risk Factors for skin cancer:

Skin that burns, freckles, reddens easily or becomes painful in the sun	No □ Yes □	Specify: Fitzpatrick type

History of sunburns, especially early in life	No □ Yes □	Specify:
Exposure to the sun through work and play	No □ Yes □	Specify:
Other	No □ Yes □	Specify:

5. Concomitant or previous medications or therapies

Immunosuppressant	No □ Yes □	Specify*
Radiations or radiotherapy	No □ Yes □	Specify *
Other	No □ Yes □	Specify*

Specify*: doses, time of exposure, indication

ID: _____ Date: _____ Gender: _____ Age: _____

1. Pharmacological anamnesis

- When did the patient start the Tildrakizumab treatment?
- Which dose of Tildrakizumab was the patient on?
- Which was the time interval from starting Tildrakizumab to the event onset?
- Which was the time interval from the last Tildrakizumab administration and the event onset?
- Specify as much as possible the cumulative Tildrakizumab dose (number of doses) received by the patient.
- Was there a positive dechallenge?
- Did the patient recover completely? No □ Yes □ Specify:

2. Patient Medical History

• Smoking	No □ Yes □	Current □ Ex □ Pack-year:
• Diabetes	No □ Yes □	Specify:
• Obesity	No □ Yes □	Specify:
• Alcohol abuse	No □ Yes □	Specify:
• HIV infection/ AIDS	No □ Yes □	Specify:

• Hepatitis	No □ Yes □	Specify:
• Tuberculosis	No □ Yes □	Specify:
• Organ transplantation	No □ Yes □	Specify:
• Immune system disorder	No □ Yes □	Specify:
• Live vaccines administration	No □ Yes □	Specify: (date/s of administration and type of vaccine/s)

3. Event:

- Which was the final **diagnosis?**
- How was the diagnosis made?
- Relevant complementary test results: Scanner, laboratory or microbiologic results.

- Outcome of the event and final **medical report**:

4. **Laboratory- tests results:**
   - Neutrophil count when the treatment was started:
   - Leucocyte count when the treatment was started:
   - Lymphocyte count when the treatment was started:

Lab-tests evolution*	Date:					
Neutrophil count: (x10^9/L)						
Leucocytes count: (x10^9/L)						
Lymphocytes count: (x10^9/L)						

*Please provide results and date of full blood count: leukocytes, neutrophil, lymphocyte counts (if available).

5. **<u>Concomitant medication for psoriasis</u>**: ☐ No ☐ Yes, if yes please specify below:

SYSTEMIC TREATMENT AND UV				**BIOLOGICS**		
	Dose (mg)	**Start** (DD/MM/YY)			**dose** (mg)	**Start** (DD/MM/YY)
☐ Cyclosporin A	|__|__|__|/d	__|__|__|__|__|__|		☐ Adalimumab	|__|__|__|	|__|__|__|__|__|__|
☐ FAEs	___ Tablets /d	|__|__|__|__|__|__|		☐ Efalizumab	|__|__|__|	|__|__|__|__|__|__|
☐ MTX	|__|__|__|/d	|__|__|__|__|__|__|		☐ Etanercept	|__|__|__|	|__|__|__|__|__|__|
☐ Retinoids	|__|__|,|__|/w	|__|__|__|__|__|__|		☐ Infliximab	|__|__|__|	|__|__|__|__|__|__|
☐ other	|__|__|,|__|/w	|__|__|__|__|__|__|		☐ Ustekinumab	|__|__|__|	|__|__|__|__|__|__|
				☐ Secukinumab	|__|__|__|	|__|__|__|__|__|__|
☐ PUVA		|__|__|__|__|__|__|		☐ Ixekizumab	|__|__|__|	|__|__|__|__|__|__|
☐ UVA/-B		|__|__|__|__|__|__|		Other:	|__|__|__|	|__|__|__|__|__|__|
				Administration: Every |__| weeks|__| x weekly		

Concomitant or previous immunosuppressant medications: ☐ No ☐ Yes à **If yes:** Please specify the medications.

Product	Daily dose	Comments (specifications)
1		
2		
3		
4		

Previous treatment for psoriasis: ☐ No ☐ Yes, if yes please specify below:

PREVIOUS treatment (multiple answers possible)					
Conventional systemic:	**Last**	**Former**	**Never**		**Duration** (months)
Cyclosporine A	☐	☐	☐		|__|__|__|
FAEs	☐	☐	☐		|__|__|__|
MTX	☐	☐	☐		|__|__|__|
Retinoids	☐	☐	☐		|__|__|__|
Leflunomide	☐	☐	☐		|__|__|__|
PUVA system	☐	☐	☐		|__|__|__|
Corticosteroids	☐	☐	☐		|__|__|__|
Other	☐	☐	☐		|__|__|__|
End of last systemic treatment			(DD/MM/YY) |__|__|__|__|__|__|		
Biologics:	**Last**	**Former**	**Never**		**Duration** (months)
Adalimumab	☐	☐	☐		|__|__|
Efalizumab	☐	☐	☐		|__|__|
Etanercept	☐	☐	☐		|__|__|
Infliximab	☐	☐	☐		|__|__|
Adalimumab	☐	☐	☐		|__|__|
Ustekinumab	☐	☐	☐		|__|__|
Secukinumab	☐	☐	☐		|__|__|
Ixekizumab	☐	☐	☐		|__|__|
Other	☐	☐	☐		|__|__|
End of last biologic treatment			(DD/MM/YY) |__|__|__|__|__|__|		

1. Pharmacological anamnesis

- Which dose of Tildrakizumab was the patient on?
- Which was the time interval from starting Tildrakizumab to the event onset?
- Which was the time interval from the last Tildrakizumab administration and the event?
- Specify as much as possible the cumulative Tildrakizumab dose (number of doses) received by the patient.
- Was there a positive dechallenge?
- Did the patient recover completely? No □ Yes □ Specify:

2. Event of depression or SIB

• Which is **the final diagnosis**? Specify:
• How was the diagnosis made? Specify: (initial symptoms / date / Psychiatric diagnosis)
• Please provide the **treatment** details and a **summary of medical report:**

3. Risk Factors for depression or SIB:

• Age:		• Gender:	
• Family history of depression	No □ Yes □		
• Personal history of depression	No □ Yes □		
• Personal history of psychiatric disorder	No □ Yes □		
• Obesity	No □ Yes □	BMI:	
• Alcohol consumption /abuse:	No □ Yes □	Current □	Ex □ Drinks/day/type:
• Illicit drug use	No □ Yes □	Specify*:	

• Other chronic diseases: liver, renal, GI, respiratory, immunological, pain, malignancy etc.	No □ Yes □	Specify*:

*Specify: (when it started, happened, or if it is on-going? Its severity, etc…

4. Specific or potential trigger factors for major depression or SIB:

• Untreated /uncontrolled psychiatric disorder	No □ Yes □	Spec
• Chronic incurable/untreatable disease	No □ Yes □	Specify:
• Illicit drug abuse	No □ Yes □	Specify:
• Alcohol consume abuse	No □ Yes □	Specify:
• Familiar or partner problems	No □ Yes □	Specify:

• Legal or social problems	No □ Yes □	Specify:
• Economic problems	No □ Yes □	Specify:
• Work problems	No □ Yes □	Specify:
• Physical disability	No □ Yes □	Specify:
• Other	No □ Yes □	Specify:

5. Concomitant or previous medications or therapies

Anti-depressive medications	No □ Yes □	Specify*
Antipsychotic medications	No □ Yes □	Specify *
Other	No □ Yes □	Specify*

Specify*: doses, time of exposure, indication

Report: o Initial Follow-up o1st o 2nd o Other: _ _

1- GENERAL INFORMATION

Country:	Source: o Clinical Trial o Spontaneous o Other: specify _ _ _ _ _ _ _ _ _ _ _	Protocol No: EUDRACT No: Blinded trial? o No o Yes: treatment code broken? o No o Yes: if yes, Unblinding result: _ _ _ _ _ _ _ _ _ _ _ _
Reporter: o Investigator o Health Care Professional	o Regulatory Authority o Consumer o Other: specify _ _ _ _ _ _ _ _ _ _ _	
If the subject/patient is in a clinical trial, has she been withdrawn from the trial? o No o Yes. Date of withdrawal _ _ / _ _ _ / _ _ _ _ dd mmm yyyy		

2- SUBJECT / PATIENT (Details of the mother)

Initials	Subject identification No.	Randomization No.	Age (years)	Date of birth
❑ Privacy ❑ Unknown	Investigator's No. / Screening No.			_ _ / _ _ _ / _ _ _ _ dd mmm yyyy

Ethnicity:	Race:	Weight
o Hispanic or latino o Not hispanic or latino	o White o Asian o Black /African American o Native Hawaiian/Other Pacific Islander o American Indian/Alaskan native o Unknown o Other_ _ _ _ _ _ _ _ _	o kg o lb .
		Height o m o ft .

Maternal medical history:

Risk factors: oDiabetes oHigh blood pressure oSmoking oAlcohol oOther, specify _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Previous pregnancies: o Yes. If yes, number: _ _ o No

Any complication during previous pregnancies: o Yes, specify below: o No

T (Term births: after 37 weeks gestation) = A (Abortions) =

P (Premature births: 20 to 37 weeks gestation) = L (Living children) =

Other relevant details on maternal medical history:

3- PATERNAL INFORMATION

Not available o

Age: __ __ years. Relevant medical history and medication:

4- DRUG EXPOSURE DURING PREGNANCY

Medication (*) (Trade name preferably)	Treatment condition (**)	Dosage regimen	Route	Administration dates			Indication for use	Interaction with drug? (****)
				Start date (dd/mmm/yyyy)	Stop date (dd/mmm/yyyy)	Cont(***)		
1. o S	o C o H			_ _/ _ _ _/ 20 _ _	_ _/ _ _ _/ 20 _ _	o		o
2. o S	o C o H			_ _/ _ _ _/ 20 _ _	_ _/ _ _ _/ 20 _ _	o		o
3. o S	o C o H			_ _/ _ _ _/ 20 _ _	_ _/ _ _ _/ 20 _ _	o		o
4. o S	o C o H			_ _/ _ _ _/ 20 _ _	_ _/ _ _ _/ 20 _ _	o		o
5. o S	o C o H			_ _/ _ _ _/ 20 _ _	_ _/ _ _ _/ 20 _ _	o		o

( ) Tick the box "S" if you suspect there is a reasonable possibility the event may have been caused by this medication*

*(**) **Treatment condition**: C= Concomitant, H=Relevant previous medication (not concomitantly administered)*

(***) Tick the box if medication has not been stopped.

*(****) **Suspected interaction:** if any interaction is suspected, please tick relevant boxes*

5- PREGNANCY INFORMATION

Trimesters of exposure:	Last menstrual period:	Estimated delivery date:	Contraceptive method?
o First o Second o Third	_ _/ _ _ _ / 20_ _ dd mmm yyyy	_ _/ _ _ _ / 20_ _ dd mmm yyyy	o Yes: specify_ _ _ _ _ _ _ _ o No o Unknown

Is the foetus developing well? o Yes o Unk o No: specify in narrative

Pregnancy associated adverse event(s)

Adverse Event(s) (Diagnosis preferable, if not available signs/symptoms. Most relevant, first)	Onset of event (dd/mmm/yyyy)	Date of resolution (dd/mmm/yy)	Outcome (*) (1-6)	Severity (**) (1-3)	Seriousness (If **yes**, complete section below)	Causality with drug (***)(1-4)
1.	_ _/ _ _ _/ _ _	_ _/ _ _ _/ _ _			o Yes o No	
2.	_ _/ _ _ _/ _ _	_ _/ _ _ _/ _ _			o Yes o No	
3.	_ _/ _ _ _/ _ _	_ _/ _ _ _/ _ _			o Yes o No	
4.	_ _/ _ _ _/ _ _	_ _/ _ _ _/ _ _			o Yes o No	

*(*) **Outcome**: 1= Recovered, 2= Recovering, 3= Not recovered 4= Recovered with sequelae (indicate sequelae in the narrative section), 5= Fatal, 6= Unknown*
*(**) **Severity scale:** 1=Mild; 2= Moderate; 3= Severe*
*(***) **Causality assessment:** 1= Not related, 2= Unlikely related, 3= Possibly related, 4= Related*

SERIOUSNESS CRITERION (tick all applicable boxes that apply for the mother)

o Fatal →	Mother date of death		Cause of death:
o Life-threatening	_ _ / _ _ _ / _ _ _ _		
o Hospitalisation or its prolongation	dd mmm yyyy		
o Persistent or significant disability or incapacity			
o Congenital anomaly or birth defect (If **yes**, indicate this information in section 6)	Autopsy performed?	o Yes o No	Report available? o Yes o No
o Other important medical event			

Narrative:

Tests performed (e.g. foetal ultrasound, amniocentesis, toxoplasmosis serology, diagnosis of adverse events)?
o No o Yes (complete section below) o Unk

Test performed	Date (dd/mmm/yyyy)	Findings / results (units) (Indicate if not yet available)	Normal range (units) (if applicable)
1.	_ _ / _ _ _ / _ _ _ _		
2.	_ _ / _ _ _ / _ _ _ _		
3.	_ _ / _ _ _ / _ _ _ _		

6- PREGNANCY OUTCOME AND NEWBORN INFORMATION

Date of birth / outcome: _ _ / _ _ _ / _ _ _ _ dd mmm yyyy	Gestational age: _ _ weeks	Outcome: o Healthy new-born o New-born abnormality o New-born death o Foetal death	o Spontaneous abortion o Elective abortion o Unknown o Ectopic pregnancy
Sex: o girl o boy o unk	Weight: _ _ _ _ grams	Height: _ _ , _ o cm o in	

Comment: (Malformation/anomalies at birth. APGAR score at 1' and 5'. Need for resuscitation or Intensive Care Unit. Neonatal illness, results of autopsy, AEs in neonate.)

Adverse Event(s) (Diagnosis preferable, if not available signs/symptoms. Most relevant, first)	Onset of event (dd/mmm/yyyy)	Date of resolution (dd/mmm/yy)	Outcome (*) (1-6)	Severity (**) (1-3)	Seriousness (If **yes**, complete section below)	Causality with drug (***) (1-4)
1.	_ _ / _ _ _ / _ _	_ _ / _ _ _ / _ _			o Yes o No	
2.	_ _ / _ _ _ / _ _	_ _ / _ _ _ / _ _			o Yes o No	
3.	_ _ / _ _ _ / _ _	_ _ / _ _ _ / _ _			o Yes o No	
4.	_ _ / _ _ _ / _ _	_ _ / _ _ _ / _ _			o Yes o No	

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*(*) **Outcome**: 1= Recovered, 2= Recovering, 3= Not recovered 4= Recovered with sequelae (indicate sequelae in the narrative section), 5= Fatal, 6= Unknown*

*(**) **Severity scale:** 1=Mild; 2= Moderate; 3= Severe*

*(***) **Causality assessment:** 1= Not related, 2= Unlikely related, 3= Possibly related, 4= Related*

Are supplemental pages attached? o No o Yes: Indicate the number of pages attached __ __

7-SOURCE

Reporter / Investigator's name:	Signature:	Date:
		_ _ / _ _ _ / 20 _ _ dd mmm yyyy

Annex 6: Details of proposed additional risk minimisation activities (if applicable)

Not applicable. Not additional risk minimisation activities planned.