Protocol title	Observational study to assess the effectiveness, safety profile and real-life prescribing and utilization patterns of tildrakizumab (Ilumetri®) in patients with moderate to severe plaque psoriasis in routine clinical practice.
Protocol ID	NIS Study M/14745/43
Medicinal Product:	Ilumetri®, 100 mg
Active Substance:	Tildrakizumab
Study Phase	Non-Interventional Study
Document status/Version	Final, Amendment II
Date	13 October 2020
Marketing Authorization Holder/ Sponsor	Almirall S.A.

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1 SIGNATURE PAGE FOR THE SPONSOR / MARKETING AUTHORIZATION HOLDER.

Study title:	Observational study to assess the effectiveness, safety profile and real-life prescribing and utilization patterns of tildrakizumab (Ilumetri®) in patients with moderate to severe plaque psoriasis in routine clinical practice
Medicinal Product:	Ilumetri®
Active Substance:	Tildrakizumab
Protocol number:	NIS Study M/14745/43
Marketing authorization holder:	Almirall S.A. (hereinafter called Almirall)

Approval of the final Non-interventional Study Protocol:

PPD

2 SIGNATURE PAGE FOR THE STUDY PHYSICIAN

Study title:	Observational study to assess the effectiveness, safety profile and real-life prescribing and utilization patterns of tildrakizumab (Ilumetri®) in patients with moderate to severe plaque psoriasis in routine clinical practice
Medicinal Product:	Ilumetri®
Active Substance:	Tildrakizumab
Protocol number:	NIS Study M/14745/43
Marketing authorization holder:	Almirall S.A.

I agree to the terms and conditions relating to this non-interventional study (NIS) as defined in this Study Protocol, electronic Case Report Form (eCRF), and any other protocol-related documents. I fully understand that any changes instituted by the study physician without previous agreement with the sponsor would constitute a violation of the study protocol.

I agree to obtain approval by an Ethics Committee or Institutional Review Board (EC/IRB) prior to study start and signed informed consent form (ICF) from all patients included in this study. In addition, I will allow direct access to source documents and agree to inspection by auditors from the sponsor and Health Authorities. Furthermore, I confirm herewith that the sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to the Worldwide Health Authorities.

_____ _____

Name Study Physician (capital letters) Signature Date

Name Institution (capital letters) _____

PROTOCOL CHANGES LOG

Amendment II, dated 13 October 2020

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20EC of the European Parliament and the Council of the European Union.

Please find below an overview of relevant changes that are made to the protocol in the course of Amendment II. In addition, to accommodate sites that have changed their routine care to involve virtual visits, the wording in 'routine practice' has been changed to 'in routine practice including virtual visits and assessments, if applicable' in the first paragraph of relevant sections.

<table>
<tr><th>Section Reference</th><th>Old text</th><th>Amended text</th></tr>
<tr><td>Protocol Signature Page</td><td>PPD</td><td>PPD
PPD</td></tr>
<tr><td>Synopsis</td><td><table><tr><td>CENTERS / COUNTRIES</td><td>Multicenter, multinational Study
This study is planned to be conducted in Germany, Denmark, Austria, The Netherlands, United Kingdom, Spain, and Italy</td></tr></table></td><td><table><tr><td>CENTERS / COUNTRIES</td><td>Multicenter, multinational Study
This study is planned to be conducted in Germany, Belgium, Austria, The Netherlands, United Kingdom, France, and Italy.</td></tr></table></td></tr>
</table>

Synopsis	PHASE: **Phase 4**, Non Interventional Study (NIS)	PHASE: ~~Phase 4~~, Non-Interventional Study (NIS)
8.3: Documentation of other, non-fatal SAEs	Other, non-fatal, SAEs will be recorded in the eCRF.	**Non-serious ADRs have to be reported within 3 business days via the ADR report form.** Other, non-fatal, SAEs will be recorded in the eCRF **only**.
7.5.3.6: Reasons for changing tildrakizumab dose	Also the number of patients changing the dose (if any) **should** be documented.	~~Also~~ The number of patients changing the dose (if any) **will** be documented. **The study physician is asked to document the reason(s) for changing the dosage of tildrakizumab (100 mg vs 200 mg), if applicable.**

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4 LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
BMI	Body Mass Index
BP	Blood Pressure
BSA	Body Surface Area
CRO	Contract Research Organization
DLQI	Dermatology Life Quality Index
DLQI-R	Dermatology Life Quality Index adjusted for not relevant responses
EC	Ethics Committee
eCRF	Electronic Case Report Form
EOS	End of Study
ET	Early Termination
FAS	Full Analysis Set
FG	Fasted Glucose
GDPR	General Data Protection Regulation
HbA1c	Hemoglobin A1c
ICF	Informed Consent Form
IL	Interleukine
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MetS	Metabolic Syndrome
NIS	Non-Interventional Study
PASI	Psoriasis Area and Severity Index
PGA	Physician Global Assessment
PR	Pulse Rate
RR	Respiration rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
TG	Triglyceride

TSQM	Treatment Satisfaction Questionnaire for Medication
WHO	World Health Organization

5 PROTOCOL SYNOPSIS

TITLE	Observational study to assess the effectiveness, safety profile and real-life prescribing and utilization patterns of tildrakizumab (Ilumetri®) in patients with moderate to severe plaque psoriasis in routine clinical practice.
PHASE	Non-Interventional Study (NIS)
CENTERS / COUNTRIES	Multicenter, multinational Study This study is planned to be conducted in Germany, Belgium, Austria, The Netherlands, United Kingdom, France, and Italy.
INVESTIGATIONAL DRUG and DOSAGE FORM	100 mg/200 mg tildrakizumab (Ilumetri®) Pre-filled syringe with 1ml injectable solution containing 100 mg tildrakizumab
ROUTE OF ADMINISTRATION	Subcutaneous injection
OBJECTIVES	Primary Objective: • To assess the effectiveness and maintenance of response of tildrakizumab (Ilumetri®) treatment in routine clinical practice Secondary Objectives: • To describe the profile of the patients who start treatment with tildrakizumab (Ilumetri®) • Correlation between absolute PASI scores and Dermatology Life Quality Index (DLQI)-R • To evaluate changes in body weight, waist and hip circumference, BMI and arterial blood pressure • To evaluate changes in food intake, physical activity and lipid blood parameters • To evaluate tolerability of Ilumetri® in patients with moderate to severe plaque psoriasis • To evaluate prescribing and utilization patterns of 2 doses of tildrakizumab (100 mg and 200 mg, if appropriate), understanding factors that influence the study physician decision making regarding the tildrakizumab dose • To assess treatment satisfaction from the study physician's and patient's perspective and to describe reasons for therapy discontinuation • To assess long term safety profile of tildrakizumab in real life clinical setting
DESIGN	This is an observational, non-interventional, multicenter study with tildrakizumab (Ilumetri®) in patients with moderate to severe plaque-psoriasis in routine practice including virtual visits and assessments, if applicable.

	In this study, patients will be assigned to one of two cohorts: • Cohort 1: patients who completed tildrakizumab clinical trials • Cohort 2: newly tildrakizumab prescribed patients In this study, the visit structure is not defined by the study protocol, but is driven by routine clinical practice in accordance to the SmPC including virtual visits and assessments, if applicable. Ideally, the visit structure will be as follows: <u>Visit structure for Cohort 1:</u> • Visit 1: Week 0/Day 0 (first injection) • Visit 2: ~ Week 12 • Visit 3: ~ Week 24 • Visit 4: ~ Week 36 • Visit 5: ~ Week 48 • Visit 6: ~ Week 60 • Visit 7: ~ Week 72 • Visit 8: ~ Week 84 • Visit 9: ~ Week 96 (EOS) <u>Visit structure for Cohort 2:</u> • Visit 1: Week 0/Day 0 (first injection) • Induction Visit: Week 4 (second injection) • Visit 2: ~ Week 16 • Visit 3: ~ Week 28 • Visit 4: ~ Week 40 • Visit 5: ~ Week 52 • Visit 6: ~ Week 64 • Visit 7: ~ Week 76 • Visit 8: ~ Week 88 • Visit 9: ~ Week 100 (EOS) A follow-up evaluation will be performed 12 weeks after last injection by phone call or during patient´s visit at the physician´s office/clinic to evaluate (S)AEs, (S)ADRs and severe infections. Extra visits may be performed during the study as needed. Relevant data from assessments routinely performed in the course of these unscheduled visits will also be recorded. Duration of the study will be approximately 2 years.
TREATMENTS	Each newly prescribed patient should receive tildrakizumab (Ilumetri®) by subcutaneous injections at Weeks 0, 4 and every 12 weeks thereafter, according to the SmPC. For patients who completed (extension) studies with tildrakizumab, no induction period is needed.

SUMMARY OF STUDY DESIGN	Tildrakizumab (Ilumetri®) is a monoclonal antibody designed for the treatment of immunologically mediated inflammatory disorders. Patients participating in this study might have been already treated with tildrakizumab (Ilumetri®) for moderate to severe psoriasis in clinical trials (following the effectiveness and safety for these patients will provide long term information about handling of this medication in routine clinical practice in treatment of psoriasis) or might have just been prescribed tildrakizumab.(Ilumetri®). After establishing the diagnosis and the therapy decision is made by the physician as well as agreed by the patient, patients can be considered eligible for participation in the observational study. Approximately 430 patients are planned to be enrolled in the study. These patients will be assigned either to Cohort 1 (patients who completed tildrakizumab clinical trials) or Cohort 2 (newly tildrakizumab prescribed patients). At baseline, routine physical examination parameters including vital signs (blood pressure, pulse rate, respiration rate, temperature) and height/weight measurements (body height, weight, BMI, waist and hip circumference (optional), waist/hip ratio (optional)) will be captured. Furthermore, anamnesis including psoriasis history and comorbidities will be performed. Optional, blood analysis results (total cholesterol, HDL-c, LDL-c, VLDL-c, TG, lipoprotein (a), MetS-HbA1c, FG) as well as urine analysis results will be registered (only if routinely performed). The observational period will start after patients´ signing the Informed Consent Form (ICF) and will end 12 weeks after last injection (follow-up evaluation). In this study, the visit structure is not defined by the study protocol, but is driven by routine clinical practice in accordance to the SmPC. Ideally, study visits will be captured as follows: • Cohort 1: therapy at Week 0/Day 0 and the maintenance therapy every 12 weeks thereafter (approximately Weeks 12, 24, 36, 48, 60, 72, 84, and 96). • Cohort 2: induction therapy at Week 0/Day 0 and Week 4, and the maintenance therapy every 12 weeks thereafter (approximately Weeks 16, 28, 40, 52, 64, 76, 88, and 100). Disease severity will be documented, if routinely done, with PASI, BSA, PGA, and Scalp/Nail PGA. Usually in clinical routine used DLQI and DLQI-R as well as VAS Itch and VAS Pain may be performed and documented at every study visit. Adverse Reactions/Events will be recorded throughout the study, as well as severe infections and blood and urine analyses results.

STUDY POPULATION	Adult male and female patients with moderate-to-severe chronic plaque psoriasis. Approximately 430 patients will be included in the study. These patients will be assigned either to Cohort 1 (patients who completed tildrakizumab clinical trials) or Cohort 2 (newly tildrakizumab prescribed patients).
INCLUSION CRITERIA	The following criteria must be met by all patients considered for study participation: 1. Written informed consent form. 2. Age ≥ 18years. 3. Moderate to severe chronic plaque psoriasis diagnosis. 4. Patients that have participated in tildrakizumab (Ilumetri®) clinical trials (Cohort 1) **OR** patients who, according to the physician's therapeutic decision, should start the treatment with tildrakizumab (Ilumetri®) (Cohort 2).
EXCLUSION CRITERIA	Patients will be excluded if they meet any of the following criteria: 1. Unable to comply with the requirements of the study or who in the opinion of the study physician should not participate in the study. 2. Patients meeting any of the exclusion criteria specified in the summary of product characteristics (SmPC) of Ilumetri® The administration of tildrakizumab (Ilumetri®) during pregnancy and lactation should be avoided as a precautionary measure. According to the SmPC, women of childbearing potential must use a reliable method of contraception during the therapy with tildrakizumab (Ilumetri®) and for 17 weeks thereafter
VARIABLES (to be documented according to clinical routine):	• Demographics (gender, age) and routine physical examination including vital signs (temperature, BP, RR, PR) and height/weight measurements (height, weight, BMI, waist and hip circumference (optional), waist/hip ratio (optional)) • Medical history: baseline disease severity (also baseline if patients participated in tildrakizumab (Ilumetri®) clinical trials), psoriasis history, comorbidities (including information from preceding tildrakizumab clinical trials, if relevant) • Prior and concomitant psoriasis therapy (last 5 years), prior and concomitant non-psoriasis therapy (last 6 months), systemic psoriasis and non-psoriasis therapy (including info from preceding tildrakizumab clinical trials if relevant) • Laboratory assessments: optional available lipid parameters

	(total cholesterol, HDL-c, LDL-c, VLDL-c, TG, lipoprotein (a)), bloods linked to MetS – HbA1c and FG, if routinely performed • Study physician´s assessments o PASI o BSA o PGA o Nail PGA o Scalp PGA o Study physician´s satisfaction with therapy • Patient´s questionnaires: o DLQI and DLQI-R o Pain and itch (VAS) o Patient´s satisfaction with therapy (TSQM [19]) o Patient questionnaires (food intake, physical activity, alcohol and cigarette consumption) • Physician´s decision criteria to start the therapy with tildrakizumab (Ilumetri®) • Tolerability, AEs, SAEs, ADRs • Drug survival • Patient adherence • Factors that influence the study physician´s decision regarding the dose (100 mg or 200 mg, if appropriate) of tildrakizumab (option based scale) • Number and proportion of patients withdrawing from the study • Number of patients changing the dose (if any)
STATISTICAL METHODOLOGY	<u>Statistical Analyses Populations:</u> There will be two analyses populations in this study: • Full Analyses Set (FAS), defined as all those patients in safety population that had at least some effectiveness data. • Safety population, defined as all patients for whom it is known that they had at least one tildrakizumab (Ilumetri®) dose during the study duration. <u>Statistical analyses:</u> Descriptive summary statistics will be provided for all effectiveness endpoints over time based on observed data (without imputation for missing data). Multiple Imputation analysis will be conducted as a sensitivity analysis. These analyses will be based on FAS population. For safety, number and percentage of patients with any Adverse Event will be provided. These analyses will be based on Safety Population. <u>Sample Size:</u>

	The maximum total number of patients to be included in this study will be 430. The patients will be assigned to one of the following cohorts: • Cohort 1: patients who completed tildrakizumab clinical trials • Cohort 2: newly tildrakizumab prescribed patients All patients meeting all of inclusion and none of exclusion criteria may be included in the study in every participating site. Due to the exploratory nature of this study, this maximum number of patients has been considered enough to meet the objectives of the study. <u>Interim Analysis:</u> An interim analysis will be performed after 150 patients completed Visit 5.

Table 5-1: Visit and Assessment Schedule based on SmPC

Visit(s) [a)]		**1 (Baseline)**		**2 - 8**	**9 (EOS)**	**Early Termination Visit (ET)**	**Follow-up Evaluation**
approximate week of study [b)]	**patients who completed tildrakizumab clinical trials**	**0 (Day 0)**	**N.A.**	**12, 24, 36, 48, 60, 72, 84**	**96**	**N.A.**	**12 Weeks after last Injection [f)]**
	newly tildrakizumab prescribed patients		**4 (Induction Visit)**	**16, 28, 40, 52, 64, 76, 88**	**100**		
Data of documentation							
Visit date (day/month/year)		X	X	X	X	X	
Inclusion/Exclusion criteria		X					
Informed consent		X					
Demographic data (age, gender)		X					
Height		X					
Routine physical examination parameters including vital signs (temperature, BP, RR, PR) and weight measurements (weight, BMI, waist and hip circumference (optional), waist/hip ratio (optional))		X	X	X	X	X	
Anamnesis/medical history incl. psoriasis history, comorbidities (including information from preceding tildrakizumab clinical trials if relevant)		X					

Visit(s) [a]		1 (Baseline)		2 - 8	9 (EOS)	Early Termination Visit (ET)	Follow-up Evaluation
approximate week of study [b]	patients who completed tildrakizumab clinical trials	0 (Day 0)	N.A.	12, 24, 36, 48, 60, 72, 84	96	N.A.	12 Weeks after last Injection [f]
	newly tildrakizumab prescribed patients		4 (Induction Visit)	16, 28, 40, 52, 64, 76, 88	100		
Prior and concomitant medications/psoriasis therapy (systemic, topicals, etc) including info from preceding tildrakizumab clinical trials, if relevant		X					
Concomitant therapies (Psoriasis and Non-Psoriasis)			X	X	X	X	
Register blood (total cholesterol, HDL-c, LDL-c, VLDL-c, TG, lipoprotein (a), MetS – HbA1c and FG) and urine analyses results (if available) [c]		X	X	X	X	X	
Study Physician's Assessments							
Reasons for prescribing tildrakizumab (Ilumentri®), reason for choosing a dose 100 mg or200 mg, if applicable		X					
Reasons for changing tildrakizumab dose, if applicable			X	X	X		
PASI, BSA, PGA, Scalp/Nail PGA		X	X	X	X	X	
Study physician´s satisfaction with tildrakizumab therapy			X	X	X	X	

Visit(s) [a]		1 (Baseline)		2 - 8	9 (EOS)	Early Termination Visit (ET)	Follow-up Evaluation
approximate week of study [b]	patients who completed tildrakizumab clinical trials	0 (Day 0)	N.A.	12, 24, 36, 48, 60, 72, 84	96	N.A.	12 Weeks after last Injection [f]
	newly tildrakizumab prescribed patients		4 (Induction Visit)	16, 28, 40, 52, 64, 76, 88	100		
Patient's Questionnaires							
DLQI, DLQI-R, VAS Itch, VAS Pain		X	X	X	X	X	
Patient satisfaction with tildrakizumab therapy (TSQM [g])			X	X	X	X	
Patient questionnaire regarding physical activity [d] and food intake [e]		X	X	X	X	X	
Alcohol consumption		X		X	X	X	
Cigarette consumption		X		X	X	X	
Tolerability and Safety							
(S)AEs, (S)ADRs		X	X	X	X	X	X
Assessment for severe infections		X	X	X	X	X	X
Date and reason for the tildrakizumab (Ilumetri®) therapy stop and new therapy						X	

Visit(s) [a]		1 (Baseline)		2 - 8	9 (EOS)	Early Termination Visit (ET)	Follow-up Evaluation
approximate week of study [b]	patients who completed tildrakizumab clinical trials	0 (Day 0)	N.A.	12, 24, 36, 48, 60, 72, 84	96	N.A.	12 Weeks after last Injection [f]
	newly tildrakizumab prescribed patients		4 (Induction Visit)	16, 28, 40, 52, 64, 76, 88	100		
Check for completeness and consistency of patient questionnaires		X	X	X	X	X	

a) Information available at the respective visits will be captured in the observational form; diagnostic and therapeutic measures are solely at the discretion of the physician.
b) Visit windows are following clinical practice and will allow a systemic assessment of observed data. The timing of the study visits is in accordance with and based on the SmPC for Ilumetri® and routine clinical practice.
c) Fasting serum total cholesterol (TC), triglycerides (Tg) and high-density lipoprotein cholesterol (HDL-c) levels, Lipoprotein (a). Low-density lipoprotein cholesterol (LDL-c) value calculated according to Friedwald's equation: LDL-c =TC − (HDL-c + [Tg/5]) [20].
d) The extent of physical activity is captured in terms of stable or more or less physical activity (minutes / day) during the observational study. Type of physical activity (tick box).
e) Food consumption: restrictions to an upper calory limit intake per day: yes no / other diet yes: specify type of diet/ etc.
f) A follow-up evaluation will be performed 12 weeks after last injection by phone call or during patient´s visit at the physician´s office/clinic to evaluate (S)AEs, (S)ADRs and severe infections.
g) Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes. 2004;2:12. Those seeking information regarding or permission to use the TSQM are directed to IQVIA at www.iqvia.com/TSQM or TSQM@iqvia.com (see also [19])

Table 5-2: Study Medication Administration Schedule based on SmPC

	Administration of tildrakizumab (Ilumetri®)									
patients who completed tildrakizumab clinical trials	Week 0/Day 0 (1st injection)		Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96
Patients newly prescribed tildrakizumab	Week 0/Day 0 (1st injection)	Week 4	Week 16	Week 28	Week 40	Week 52	Week 64	Week 76	Week 88	Week 100
	Visit 1	**Induction Visit**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**

6 INTRODUCTION AND RATIONALE

6.1 Introduction

6.1.1 Psoriasis

Psoriasis is a chronic immune mediated disease affecting the skin and joints. It affects an estimated 7.8 million adults in Europe and approximately 125 million people worldwide [3]. It is a non-contagious disorder that accelerates the growth cycle of skin cells and results in thickening and scaling of skin areas. The most common form of psoriasis, called plaque psoriasis, appear as red, raised areas of skin covered with flaky white scales, which may be itchy and painful and can crack and bleed. Despite different treatment options existing, many people with plaque psoriasis continue to struggle with the ongoing, persistent nature of this chronic disease.

6.1.2 Tildrakizumab (Ilumetri®)

Tildrakizumab is a humanized IgG1/k monoclonal antibody, which specifically binds to the p19 protein subunit of the interleukin-23 (IL-23) cytokine [16] and inhibits its interaction with the IL-23 receptor. Ilumetri® an anti-IL-23p19 monoclonal antibody is indicated for the treatment of patients with moderate to severe plaque psoriasis plaque psoriasis who are candidates for systemic therapy [9].

IL-23 is a naturally occurring cytokine involved in inflammatory and immune responses. Structurally, IL-23 is a heterodimer composed of a unique p19 subunit (IL-23p19) and a p40 subunit, common for IL-23 and IL-12 [13, 1]. In in vitro models, tildrakizumab was shown to disrupt IL-23 mediated signaling and cytokine cascades by disrupting the interaction of IL-23 binding to its specific receptor, IL-23R without binding to IL-12.

Identification of key cytokines such as IL-17 and IL-23 as the central axes driving the immune pathway in psoriasis has led to immunotherapy that specifically targets these ILs(12) [16]. Regarding its biological role, IL-23 is essential in the enhancement of memory T-cells, regulation of antibody production, induction of IFN-γ and proliferation of Th17 cells secreting IL-17 and IL-22, contributing to immune response against infection, but also is attributed a pathogenic role in autoimmune diseases and cancers [21, 2, 18]. In addition, there are studies suggesting that alleles around gene regions that encode IL-23 (IL23A, IL12B) and the IL-23R increase significantly the risk of psoriasis [5, 12, 1]. In psoriasis skin lesions, Th17 cells and IL-23 are abundant, exerting pro-inflammatory effects, and both IL-23 p19 and p40 subunits are over-expressed [2].

Following completion of the phase III reSURFACE trials, tildrakizumab was approved by the EMA on September 2018 for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy [9].

Both studies, reSURFACE 1 and 2, show for both Tildrakizumab 100 mg and 200mg that around 61% - 66% of patients achieved 75% of skin clearance (Psoriasis Area Sensitivity Index or PASI 75) by week 12 and 73-79% at week 28 after only 3 doses. Moreover, 49 %-57% of patients achieved PASI 90 (90% of skin clearance) and 22 %-31 % reached PASI 100 (100% of skin clearance) at week 28. More than 50% of patients reported that psoriasis no longer affected their lives after only 3 doses [14, 9]. Ninety-two percent (92 %) of patients who had achieved a PASI 75 response at 28 weeks maintained their PASI 75 response to tildrakizumab after one year of therapy.

Moreover, the results of a pooled analysis through 3 years from both studies show the consistent maintenance of efficacy and safety over 3 years of tildrakizumab (Ilumetri®) in patients with moderate-to-severe chronic plaque psoriasis who were PASI 75 responders at week 28 [17]. A PASI 75 response was maintained with continued treatment with tildrakizumab (Ilumetri®) in 9 out of 10 patients up to week 148. Tildrakizumab (Ilumetri®) was well-tolerated with very low drug-related serious adverse events and discontinuation rates. The most common (> 1.0%) adverse drug reactions (ADRs) were upper respiratory infections, headache, gastroenteritis, nausea, diarrhea, injection site pain and back pain.

Data from long-term extension studies and real word data are needed to fully explore treatment efficacy and maintenance of response as well as safety profile of anti–IL-23p19 agents for the treatment of moderate to severe psoriasis in routine practice. Tildrakizumab was the first anti p19/IL-23 monoclonal antibody to initiate phase 3 clinical development in psoriasis, with long-term safety studies that have been extended until the product has been commercially available [7, 8,]. Therefore, this study will provide the opportunity to continue the follow-up of these patients treated for more than 4 years in clinical trials and therefore provide the longest long-term data available for this new class of monoclonal antibodies. In addition, the study will help to confirm the efficacy, maintenance of response and safety profile on new patients under routine clinical care.

It is well understood, that patients with psoriasis have a higher prevalence of cardio-metabolic risk factors compared to the overall population [10]. Underlying conditions are high body weight, body mass index and altered lipid metabolism in patients with psoriasis. Obesity may contribute to an elevated risk of developing immune mediated inflammatory diseases, and vice versa 10 to 50 % of patients with immune mediated inflammatory diseases are obese [4].

Consequent reduction of lipid intake and/ or lipid-lowering medication are fundamental preventative and therapeutic measures to reduce atherosclerosis together with diet, physical exercise, and smoking cessation. Hence, together with the onset of a new systemic anti-inflammatory treatment in patients with plaque psoriasis it is of interest to investigate the dynamic profile of lipid serum parameters, together with other known risk factors which are measured in daily routine.

6.2 Study Rationale

The present study will be conducted to gain further long-term data on effectiveness and maintenance of response of tildrakizumab (Ilumetri®) in a study population when treated under routine clinical conditions. This study will help to obtain further understanding on real-life prescribing and utilization patterns of tildrakizumab (Ilumetri®) in patients with moderate to severe plaque psoriasis who completed tildrakizumab studies as well as new tildrakizumab patients. Safety data in tildrakizumab treated patients will be collected as well. Moreover, the therapy adherence to tildrakizumab (Ilumetri®), i.e., the “drug survival”, which will allow to evaluate its effectiveness, safety and physician’s/patient’s treatment satisfaction and used as an indicator of treatment success, will be evaluated.

Changes in physical activity as well as changes in diet will be captured to estimate the effect of physical activity on the body weight, BMI and arterial blood pressure. Changes in diet and food intake will be generally captured, to rule out that an accompanying new diet or changed food intake quantities are responsible for weight loss or gain and BMI changes.

Additional factors that may be related to obesity, such as accompanying depression are captured by co-medication assessment indirectly.

In this study, patients will be assigned to one of two cohorts. While Cohort 2 will include newly tildrakizumab prescribed patients, Cohort 1 will include patients who completed previous Phase 3 tildrakizumab clinical trials and extension studies. In the scope of this NIS a continued observation of these patients will allow to collect long term safety data as well as long term effectiveness data over several years in total. Additionally, it will be ascertained how real-world conditions impact the effectiveness of tildrakizumab (Ilumetri®) compared to the treatment under defined conditions in the Phase 3 (extension) studies.

7 STUDY OBJECTIVES

The present study will be conducted to gain further data on effectiveness and safety of tildrakizumab (Ilumetri®) in patients treated in routine clinical care including virtual visits and assessments, if applicable. Moreover, this study will help to obtain further understanding on real-life prescribing and utilization patterns of tildrakizumab (Ilumetri®) in patients with moderate to severe plaque psoriasis who completed tildrakizumab clinical trials and extension studies as well as newly tildrakizumab prescribed patients.

The potential effect of tildrakizumab (Ilumetri®) on body weight, waist and hip circumference, BMI, and arterial BP will be evaluated as well. An optional evaluation will be performed on serum lipids (total cholesterol, HDL-c, LDL-c, VLDL-c, TG, lipoprotein (a)). Furthermore, changes in food intake and physical activity will be assessed.

Additionally, the influence of tildrakizumab (Ilumetri®) on health-related quality of life and therapy satisfaction will be evaluated.

7.1 Primary Objective:

- To assess the effectiveness and maintenance of response of tildrakizumab (Ilumetri®) treatment in routine clinical practice

7.2 Secondary Objectives:

- To describe the profile of the patients who start treatment with tildrakizumab (Ilumetri®)
- Correlation between absolute PASI scores and Dermatology Life Quality Index (DLQI)-R
- To evaluate changes in body weight, waist and hip circumference, BMI and arterial blood pressure
- To evaluate changes in food intake, physical activity and lipid blood parameters
- To evaluate tolerability of tildrakizumab (Ilumetri®) in patients with moderate to severe plaque psoriasis
- To evaluate prescribing and utilization patterns of 2 doses of tildrakizumab (100 mg and 200 mg, if appropriate), understanding factors that influence the study physician decision making regarding the tildrakizumab dose
- To assess treatment satisfaction from the study physician's and patient's perspective and to describe reasons for therapy discontinuation
- To assess long term safety profile of tildrakizumab in real life clinical setting

7.3 Outcome Parameters

7.3.1 Primary Outcome Parameters

Cohort 1 (Subgroup of patients continuing treatment with tildrakizumab):

- Absolute PASI scores and change from baseline value at Visit 5 and Visit 9 (EOS)
- Correlation between absolute PASI scores and DLQI-R at Visit 5 and Visit 9 (EOS)
- Percentage of patients maintaining PASI 75, 90, 100 responses at Visit 5 and Visit 9 (EOS) (re-SURFACE studies (if available) and Week 0/Day 0 of SAIL study)
- Absolute BSA and change of BSA from baselines (reSURFACE and SAIL) at Visit 5 and Visit 9 (EOS)

- Absolute PGA (general, nail, scalp) and change from baseline values (reSURFACE and SAIL) at Visit 5 and Visit 9 (EOS)

Cohort 2 (Newly prescribed patients):

- Absolute PASI scores and change from baseline value at Visit 5 and Visit 9 (EOS)
- Correlation between absolute PASI scores and DLQI-R at Visit 5 and Visit 9 (EOS)
- Percentage of patients achieving PASI 75, 90, 100 at Visit 5 and Visit 9 (EOS)
- Absolute BSA and change from baseline value at Visit 5 and Visit 9 (EOS)
- Absolute PGA (general, nail, scalp) and change from baseline value at Visit 5 and Visit 9 (EOS)

7.3.2 Secondary Outcome Parameters

- Absolute DLQI and DLQI-R score and change from baseline value at Visit 5 and Visit 9 (EOS)(both baselines for continuing patients if data available)
- Absolute VAS (patient and physician´s satisfaction with therapy, pain and itch) scores and change from baseline (both baselines for continuing patients if data available)
- Proportion of patients adding concomitant medications from baseline at Visit 5 and Visit 9 (EOS)
- Changes in weight measurements (body weight, waist and hip circumference, waist/hip ratio, BMI) and blood pressure from baseline at Visit 9 (EOS) or Early Termination
- Changes in food intake: quantitative and qualitative from baseline up to Visit 9 (EOS) or Early Termination.
- Changes in physical activity: quantitative and qualitative from baseline up to Visit 9 (EOS).
- Changes in lipid blood parameters in patients from baseline up to Visit 9 (EOS), if routinely available.
- Number and proportion of patients withdrawing from the study.
- Number of patients changing the dose (if any) and factors that influence the study physician's decision regarding the prescription of a dose of tildrakizumab (100 mg or 200 mg, if appropriate) (option based scale)
- Drug survival up to Visit 9 (EOS)
- Patient adherence up to Visit 9 (EOS)

7.4 Overall Study Design

This is an observational, non-interventional, multicenter study according to Directive 2001/20/EC [11] in the frame of the long-term therapy with tildrakizumab (Ilumetri®) of patients with moderate to severe plaque-psoriasis in routine practice, including virtual visits and assessments, if applicable.

The treatment, including diagnosis and monitoring of patients, exclusively follows routine medical practice. The study physicians will choose the treatment independently from this NIS. In order to be able to assess the study objectives formulated above on a sufficiently large number of patients, a multicenter, non-interventional study is best suited, since only this study type allows evaluation of the therapy under practice conditions. In particular, it should be noted

that the selection of patients to be included in the NIS is made by the study physician only after his assessment of the medical utility and necessity.

All patients will be informed about the purpose and the content of the NIS. Written informed consent will be obtained from all participating patients before any data collection.

The study plan together with the written patient information and informed consent form will be submitted to the responsible Ethics Committee before study start.

Up to 430 patients will be included in this study. These patients will be assigned to one of the following cohorts:

- Cohort 1: patients who completed tildrakizumab clinical trials
- Cohort 2: newly tildrakizumab prescribed patients

Patients meeting all of inclusion and none of exclusion criteria may be included in the study in every participating site.

Due to the exploratory nature of this study, this maximum number of patients has been considered enough to meet the objectives of the study.

The study will be performed at approximately 76 study sites across seven European countries:

- Austria
- Belgium
- Germany
- Italy
- The Netherlands
- France
- UK

Each patient will be followed for approximately 2 years. Tildrakizumab will become commercially available at different time-points in the participating countries. This will lead to variation of the actual time-points of the study start from country to country. Therefore, the total study duration from the inclusion of the first patient first visit to the last patient last visit will be approximately 4 years.

Patients will not be compensated for participating in this NIS.

7.5 Study Assessments

In this NIS, the visit structure is not defined by the schedule of assessments and the visit descriptions, but is driven by routine clinical practice, including virtual visits and assessments, if applicable. Diagnostic and therapeutic procedures within the scope of this NIS are not given, but stay solely at the discretion of the treating doctor. The following descriptions reflect the structure of the eCRF.

The time windows are proposed in order to provide a systematic assessment of the data. The proposed study visit structure is based on the SmPC of tildrakizumab (Ilumetri®) and routine clinical practice.

Data collection stops for each patient at Visit 9 (EOS) or ET visit. (S)AEs, (S)ADRs, and severe infections will be evaluated until 12 weeks after last injection. No further data will be collected after ICF withdrawal.

7.5.1 Informed Consent

After adequate explanation of the aims and procedures of the study a signed, written informed consent regarding collection, evaluation, saving and transfer of the clinical data will be obtained from each patient. Patients may withdraw their consent to participate in this NIS at any time.

7.5.2 Baseline Parameters and Concomitant Medications

The following baseline and patient characteristics will be collected:

7.5.2.1 General Medical History

General medical history includes all relevant prior and concomitant diseases other than psoriasis. If applicable, all changes during the study should be documented.

7.5.2.2 Psoriasis history

Psoriasis history data to be documented at Visit 1 (baseline) include:

- Date of first diagnosis
- Presence of other simultaneous forms of psoriasis (e.g., nail or scalp psoriasis)
- Comorbidities (including info from preceding tildrakizumab clinical trials, if relevant)

7.5.2.3 Demographics

Demographic data to be documented at Visit 1 (baseline) include:

- Age
- Gender

7.5.2.4 Physical Examination

Routine physical examination will be performed including vital signs (temperature, blood pressure (BP), respiration rate (RR), pulse rate (PR)), and height/weight measurements (height, weight, BMI, waist and hip circumference (optional), waist/hip ratio (optional)).

7.5.2.5 Prior and Concomitant Medications

All concomitant medications for the treatment of concomitant diseases should be documented at Visit 1 (baseline).

Documentation of anti-psoriatic treatment should include all prior (5-year history) and concomitant topical, photo- or systemic therapies with start and stop date (if applicable).

Documentation of any other (not anti-psoriatic) treatments should include all prior (6-months history) and concomitant topical, photo- or systemic therapies with start and stop date (if applicable).

If applicable, relevant information from preceding tildrakizumab clinical studies should also be documented.

Documentation of all concomitant medications should be updated at each visit.

7.5.2.6 Treatment with tildrakizumab (Ilumetri®)

Dosing of tildrakizumab (Ilumetri®) should follow the guidance provided in the SmPC.

Study physicians should document the (planned) dates of all tildrakizumab (Ilumetri®) injections. If treatment with tildrakizumab (Ilumetri®) is stopped, the reason for discontinuation should be documented and the subsequent therapy be specified.

7.5.2.7 Blood and Urine Analyses - optional

If routinely done, the following laboratory assessments should be documented:

- Blood analysis results: blood lipids (total cholesterol, HDL-c, LDL-c, VLDL-c, TG, lipoprotein (a)), MetS – HbA1c and fasted glucose (FG)
- Urine analysis results

7.5.2.8 Reasons for prescribing tildrakizumab (Ilumetri®)

The study physician is asked to document the reason for choosing 100 mg tildrakizumab or 200 mg tildrakizumab, if applicable.

7.5.3 Study Physician's Assessments

7.5.3.1 Psoriasis Area and Severity Index (PASI)

The body is divided into four sections:

1. Head (H): 10% of a person's skin
2. Arms (A): 20% of a person`s skin
3. Trunk (T): 30% of a person`s skin
4. Legs (L): 40% of a person`s skin

Each of these areas is scored by itself, and then the four scores are combined into the final PASI. For each section, the percent of area of skin involved, is estimated and then transformed into a grade from 0 to 6:

0 = 0% of involved area
1 = < 10% of involved area
2 = 10–29% of involved area
3 = 30–49% of involved area
4 = 50–69% of involved area
5 = 70–89% of involved area
6 = 90–100% of involved area

Within each area, the severity is estimated by 3 clinical signs: erythema (redness), induration (thickness) and desquamation (scaling). Severity parameters are measured on a scale of 0 to 4, from "none" to "maximum".
The sum of all 3 severity parameters is then calculated for each section of skin, multiplied by the area score for that area and multiplied by weight of respective section (0.1 for head, 0.2 for arms, 0.3 for body and 0.4 for legs).

The possible range of the PASI is from 0 ("no psoriasis on the body") to 72 ("the most severe case of psoriasis"). PASI should be documented at each visit.

7.5.3.2 Body Surface Area (BSA)

The BSA assessment measures the total area of the body affected by psoriasis. Using the surface of the hand to equal 1% BSA, the study physician will assess the total BSA affected.

7.5.3.3 Study Physician's Global Assessment (PGA)

The PGA is a 5-point measure of psoriasis based on the degree of erythema, induration, and scale averaged over the entire body.

The PGA of psoriasis (of the whole body) will be made on a 5-point scale as follows:

0 = none (clear)
1 = minimal
2 = mild
3 = moderate
4 = severe

The final PGA score is an average of the erythema, induration, and scale

7.5.3.4 Scalp PGA

The same scale as for the whole body PGA will be used for scalp PGA. Scalp PGA should be made at Visits 1 to 9 or Early Termination Visit.

7.5.3.5 Nail PGA

The same scale as for the whole body PGA will be used by the study physician to assess the psoriasis of the nails. Nail PGA should be made at Visits 1 to 9 or Early Termination Visit.

7.5.3.6 Reasons for changing tildrakizumab dose

The study physician is asked to document his reasons for changing the dosage of tildrakizumab (100 mg vs 200 mg), if applicable. The number of patients changing the dose (if any) will be documented. The study physician is asked to document the reason(s) for changing the dosage of tildrakizumab (100 mg vs 200 mg), if applicable.

7.5.3.7 Tildrakizumab (Ilumetri®) therapy stop and new therapy, if applicable

The study physician is asked to document the date and reason for the tildrakizumab (Ilumetri®) therapy stop and to provide information regarding new therapy, if applicable.

7.5.3.8 Study Physician's Satisfaction with Therapy

Study physician's satisfaction both with regard to effectiveness and tolerability of tildrakizumab (Ilumetri®) should be documented during the study at Visits 2 - 9 or Early Termination Visit.

Both effectiveness and tolerability of tildrakizumab (Ilumetri®) should be rated on a 4-point scale ranging over "very good", "good", "acceptable" and "bad". If the tolerability is rated as "bad", the reason for this assessment should be recorded on the "Adverse Drug Reaction" form (ADR form).

7.5.4 Patients' Questionnaires

The questionnaires and scales to be completed by the patients for their assessments will be provided in their national language.

7.5.4.1 Dermatology Life Quality Index (DLQI and DLQI-R)

The DLQI questionnaire consists of 10 questions, covering the following topics: symptoms, embarrassment, shopping and home care, clothes, social and leisure, sport, work or study, close relationships, sexuality, treatment.

Each question refers to the impact of the skin disease on the patient's life over the previous week.

Each question is scored from 0 to 3, giving a possible score range from 0 (meaning no impact of skin disease on quality of life) to 30 (meaning maximum impact on quality of life).

Patients should be asked to complete this questionnaire at all visits before any examinations or assessments. After completion of the questionnaire, the study physician should check the questionnaire for completeness and consistency.

The DLQI-R is a newly introduced variation of the regular DLQI that adjusts the total score for the number of not relevant responses and seems to be a valid scoring system for avoiding the bias of these not relevant responses of the questionnaire [15].

7.5.4.2 Treatment Satisfaction Questionnaire for Medication (TSQM)

In this NIS, TSQM Version 1.4 [19] will be used to determine patient´s satisfaction with the tildrakizumab (Ilumetri®) therapy. This questionnaire is comprised of 14 items which represent the following four domains:

- Effectiveness
- Side effects
- Convenience
- Global satisfaction

TSQM scores range from 0 to 100, higher scores indicating greater satisfaction.

7.5.4.3 Assessment of Itch and Pain

Itch and pain of the skin will be assessed by the patients on visual analogue scales (VAS), where 0 represents the best possible condition ("no itching" and "no skin pain", respectively) and 100 the worst possible condition ("worst itch imaginable" and "severe skin pain", respectively).

The VAS for itch and pain should be completed by the patient (and controlled by the study physician) at all visits before any examinations or assessments.

7.5.4.4 Patient questionnaires (food intake, physical activity, alcohol and cigarette consumption)

Patients will be asked to complete a simple questionnaire regarding their food intake and physical activities as well as their alcohol and cigarette consumption at every study visit.

7.5.5 Pregnancy Test

The administration of tildrakizumab (Ilumetri®) during pregnancy and lactation should be avoided as a precautionary measure. According to the SmPC, women of childbearing potential must use a reliable method of contraception during the therapy with tildrakizumab (Ilumetri®) and for 17 weeks thereafter.

7.6 Visit Schedule

The Visit and Assessment Schedule is presented in Table 5-1.

In this study, the visit structure is not defined by the study protocol, but is driven by routine clinical practice in accordance to the SmPC, including virtual visits and assessments, if applicable. Ideally the visit structure will be as follows:

Visit structure for Cohort 1:

- Visit 1: Week 0/Day 0 (first injection)
- Visit 2: ~ Week 12
- Visit 3: ~ Week 24
- Visit 4: ~ Week 36
- Visit 5: ~ Week 48
- Visit 6: ~ Week 60
- Visit 7: ~ Week 72
- Visit 8: ~ Week 84
- Visit 9: ~ Week 96 (EOS)

Visit structure for Cohort 2:

- Visit 1: Week 0/Day 0 (first injection)
- Induction Visit: Week 4 (second injection)
- Visit 2: ~ Week 16
- Visit 3: ~ Week 28
- Visit 4: ~ Week 40
- Visit 5: ~ Week 52
- Visit 6: ~ Week 64
- Visit 7: ~ Week 76
- Visit 8: ~ Week 88
- Visit 9: ~ Week 100 (EOS)

A follow-up evaluation will be performed 12 weeks after last injection by phone call or during patient´s visit at the physician´s office/clinic to evaluate (S)AEs, (S)ADRs and severe infections.

Extra visits may be performed during the study as needed. Relevant data from assessments routinely performed in the course of these unscheduled visits will also be recorded.

Duration of the study per patient will be approximately 2 years.

Diagnostic and therapeutic procedures within the scope of this NIS are not given, but stay solely at the discretion of the treating doctor. The following descriptions reflect the structure of the eCRF.

The visit windows (included in Table 5-1) are proposed in order to provide a systematic assessment of the data. The proposed study visit structure is based on the SmPC of tildrakizumab (Ilumetri®) and routine clinical practice.
The Study Medication Administration Schedule based on the SmPC of tildrakizumab (Ilumetri®) and is outlined in Table 5-2.

Each newly prescribed patient will receive 100 mg of tildrakizumab (Ilumetri®) by subcutaneous injections at Week 0/Day 0, Week 4 and every 12 weeks thereafter. For patients coming from extension studies with tildrakizumab, no induction period is needed. Thus, patients may continue administration of tildrakizumab (Ilumetri®) by subcutaneous injections every 12 weeks.

The decision for the patient treatment by the physician has to be done independently of this NIS according to routine care.

7.6.1 Visit 1 – Baseline (Day 0/Week 0), first injection

- Prior to any documentation within the scope of this study, written informed consent must be obtained from the patient
- Check of the eligibility of the patient (in-/exclusion criteria)
- Date of visit
- Demographic data (age, gender)
- Routine physical examination including vital signs (temperature, BP, RR, PR) and height/weight measurements (weight, BMI, waist and hip circumference (optional), waist/hip ratio (optional))
- General medical history and psoriasis history, including documentation of relevant information from preceding tildrakizumab clinical trials, if applicable
- Existing forms of psoriasis
- Prior topical, photo- or systemic therapy of psoriasis (within the preceding 5 years) and prior topical, photo- or systemic non-psoriasis therapies (within the preceding 6 months)
- Concomitant anti-psoriatic and other relevant medication including relevant information from preceding tildrakizumab clinical trials, if applicable
- Only if routinely performed: Laboratory Assessments
    - Documentation of Blood analysis: lipid parameters (total cholesterol, HDL-c, LDL-c, VLDL-c, TG, lipoprotein (a)), MetS - HbA1c and FG.
    - Documentation of Urine analysis
- Patient's assessments (should be made prior to any other examinations and assessments and checked for consistency and completeness by the study physician.
    - DLQI
    - DLQI-R
    - VAS itch
    - VAS pain
    - Patient questionnaire regarding food intake and physical activity
- Check for completeness and consistency of patient questionnaires
- Study physician's assessments:
    - PASI
    - BSA
    - PGA

- scalp PGA
- nail PGA

- Reasons for prescribing 100 mg or 200 mg tildrakizumab, if applicable
- Administration of the first tildrakizumab (Ilumetri®) injection
- For newly prescribed patients:

  Patient's instruction in subcutaneous injection technique (according to package leaflet) for self-injection of Ilumetri® at Week 4 and every 12 weeks thereafter (see injection schedule in Table 5-2).
- For patients coming from clinical trials with tildrakizumab no induction period is needed. Thus, patients may continue administration of tildrakizumab every 12 weeks (see injection schedule in Table 5-2).
- Documentation of safety and tolerability
- Documentation of alcohol intake and cigarette consumption

7.6.2 Induction Visit (only for newly tildrakizumab prescribed patients)

- Date of Visit
- Routine physical examination including vital signs (temperature, BP, RR, PR)
- Concomitant anti-psoriatic and other relevant medication including relevant information from preceding tildrakizumab clinical trials, if applicable
- Only if routinely performed: Laboratory Assessments
  - Documentation of blood analysis: lipid parameters (total cholesterol, HDL-c, LDL-c, VLDL-c, TG, lipoprotein (a)), MetS - HbA1c and FG.
  - Documentation of Urine analysis
- Patient's assessments (should be made prior to any other examinations and assessments and checked for consistency and completeness by the study physician).
  - DLQI
  - DLQI-R
  - VAS itch
  - VAS pain
  - Patient questionnaire regarding food intake and physical activity
  - Patient questionnaire regarding satisfaction with tildrakizumab therapy (TSQM) [19]
- Check for completeness and consistency of patient questionnaires
- Study physician's assessments:
  - PASI
  - BSA
  - PGA
  - scalp PGA
  - nail PGA
- Study physician's satisfaction with tildrakizumab (Ilumetri®) therapy

- Administration of tildrakizumab (Ilumetri®) injection
- Documentation of safety and tolerability
- Reasons for changing dose of tildrakizumab (100 mg vs 200 mg), if applicable
- Date and reason for the tildrakizumab (Ilumetri®) therapy stop and new therapy, if applicable

7.6.3 Visit 2 - 8

- Date of visit
- Update on concomitant anti-psoriatic and other relevant medication
- Routine physical examination including vital signs (body temperature, BP, RR, PR) and weight measurements (weight, BMI, waist and hip circumference (optional), waist/hip ratio (optional))
- Only if routinely performed: Laboratory Assessments
  - Documentation of Blood analysis (if available): lipid parameters (total cholesterol, HDL-c, LDL-c, VLDL-c, TG, lipoprotein (a)), MetS - HbA1c and FG.
  - Documentation of Urine analysis (if available).
- Patient's assessments (should be made prior to any other examinations and assessments and checked for consistency and completeness by the study physician).
  - DLQI
  - DLQI-R
  - VAS itch
  - VAS pain
  - Patient questionnaire regarding food intake and physical activity
  - Patient questionnaire regarding satisfaction with tildrakizumab therapy (TSQM) [19]
- Check for completeness and consistency of patient questionnaires
- Study physician's assessments:
  - PASI
  - BSA
  - PGA
  - scalp PGA
  - nail PGA
- Study physician's satisfaction with tildrakizumab (Ilumetri®) therapy
- Administration of tildrakizumab (Ilumetri®) injection
- Documentation of safety and tolerability
- Reasons for changing dose of tildrakizumab (100 mg vs 200 mg), if applicable
- Date and reason for the tildrakizumab (Ilumetri®) therapy stop and new therapy, if applicable
- Documentation of alcohol intake and cigarette consumption

7.6.4 Visit 9 (End of Study Visit)

- Date of visit
- Update on concomitant anti-psoriatic and other relevant medication
- Routine physical examination including vital signs (body temperature, BP, RR, PR) and weight measurements (weight, BMI, waist and hip circumference (optional), waist/hip ratio (optional))
- Only if routinely performed: Laboratory Assessments
  - Documentation of Blood analysis: lipid parameters (total cholesterol, HDL-c, LDL-c, VLDL-c, TG, lipoprotein (a)), MetS - HbA1c and FG.
  - Documentation of Urine analysis
- Patient's assessments (should be made prior to any other examinations and assessments and checked for consistency and completeness by the study physician.
  - DLQI
  - DLQI-R
  - VAS itch
  - VAS pain
  - Patient questionnaire regarding food intake and physical activity
  - Patient questionnaire regarding satisfaction with tildrakizumab therapy (TSQM) [19]
- Check for completeness and consistency of patient questionnaires
- Study physician's assessments:
  - PASI
  - BSA
  - PGA
  - scalp PGA
  - nail PGA
- Study physician's satisfaction with tildrakizumab (Ilumetri®) therapy
- Administration of tildrakizumab (Ilumetri®) injection
- Documentation of safety and tolerability
- Reasons for changing dose of tildrakizumab (100 mg vs 200 mg), if applicable
- Date and reason for the tildrakizumab (Ilumetri®) therapy stop and new therapy, if applicable
- Documentation of alcohol intake and cigarette consumption

7.6.5 Early Termination Visit

This visit only applies to patients who discontinue treatment with tildrakizumab (Ilumetri®) prior to the regular end of the observation period, i.e., prior to Week 100. It should be performed as soon as possible after the decision for treatment discontinuation was made. Thereafter, the documentation in context with this NIS will be stopped.

- Date of visit

- Update on concomitant anti-psoriatic and other relevant medication
- Routine physical examination including vital signs (body temperature, BP, RR, PR) and weight measurements (weight, BMI, waist and hip circumference (optional), waist/hip ratio (optional))
- Only if routinely performed: Laboratory Assessments
  - Documentation of Blood analysis: lipid parameters (total cholesterol, HDL-c, LDL-c, VLDL-c, TG, lipoprotein (a)), MetS - HbA1c and FG.
  - Documentation of Urine analysis.
- Patient's assessments (should be made prior to any other examinations and assessments and checked for consistency and completeness by the study physician.
  - DLQI
  - DLQI-R
  - VAS itch
  - VAS pain
  - Patient questionnaire regarding food intake and physical activity
  - Patient questionnaire regarding satisfaction with tildrakizumab therapy (TSQM) [19]
- Check for completeness and consistency of patient questionnaires
- Study physician's assessments:
  - PASI
  - BSA
  - PGA
  - scalp PGA
  - nail PGA
- Study physician's satisfaction with tildrakizumab (Ilumetri®) therapy
- Documentation of safety and tolerability
- Date and reason for the tildrakizumab (Ilumetri®) therapy stop and new therapy, if applicable
- Documentation of alcohol intake and cigarette consumption

7.6.6 Extra Visits (unscheduled)

This visit only applies to patients who need any extra visits due to any discomforts appearing in the course of this study. If routinely performed, data of the following assessments will be recorded during these unscheduled visits:

- Date of Visit
- Routine physical examination including vital signs (temperature, BP, RR, PR)
- Concomitant anti-psoriatic and other relevant medication including relevant information from preceding tildrakizumab clinical trials, if applicable
- Only if routinely performed: Laboratory Assessments
  - Documentation of blood analysis: lipid parameters (total cholesterol, HDL-c, LDL-c, VLDL-c, TG, lipoprotein (a)), MetS - HbA1c and FG.

- Documentation of Urine analysis

- Patient's assessments (should be made prior to any other examinations and assessments and checked for consistency and completeness by the study physician).
  - DLQI
  - DLQI-R
  - VAS itch
  - VAS pain
  - Patient questionnaire regarding food intake and physical activity
  - Patient questionnaire regarding satisfaction with tildrakizumab therapy (TSQM) [19]
- Check for completeness and consistency of patient questionnaires
- Study physician's assessments:
  - PASI
  - BSA
  - PGA
  - scalp PGA
  - nail PGA
- Study physician's satisfaction with tildrakizumab (Ilumetri®) therapy
- Administration of tildrakizumab (Ilumetri®) injection
- Documentation of safety and tolerability
- Reasons for changing dose of tildrakizumab (100 mg vs 200 mg), if applicable
- Date and reason for the tildrakizumab (Ilumetri®) therapy stop and new therapy, if applicable
- Documentation of alcohol intake and cigarette consumption

7.6.7 Follow-up Evaluation

A follow-up evaluation will be performed 12 weeks after last injection by phone call or during patient´s visit at the physician´s office/clinic to evaluate (S)AEs, (S)ADRs and severe infections.

7.7 Study Population

The patient population will include adult male and female patients with moderate-to-severe chronic plaque psoriasis.

Up to 430 patients will be included. These patients will be assigned to one of the following cohorts:

- Cohort 1: patients who completed tildrakizumab clinical trials
- Cohort 2: newly tildrakizumab prescribed patients

Patients meeting all of inclusion and none of exclusion criteria may be included in the study in every participating site.

Due to the exploratory nature of this study, this maximum number of patients has been considered enough to meet the objectives of the study.

7.7.1 Inclusion Criteria

The following criteria must be met by all subjects considered for study participation:

1. Written informed consent form.
2. Age ≥ 18years.
3. Moderate to severe chronic plaque psoriasis diagnosis.
4. Patients that have participated in tildrakizumab (Ilumetri®) clinical trials **OR** patients who, according to the doctor's decision, should start the treatment with tildrakizumab (Ilumetri®).

7.7.2 Exclusion Criteria

Patients will be excluded if they meet any of the following criteria:

1. Unable to comply with the requirements of the study or who in the opinion of the study physician should not participate in the study.
2. Patients meeting any of the exclusion criteria specified in the summary of product characteristics (SmPC) of Ilumetri®

The administration of tildrakizumab (Ilumetri®) during pregnancy and lactation should be avoided as a precautionary measure. According to the SmPC, women of childbearing potential must use a reliable method of contraception during the therapy with tildrakizumab (Ilumetri®) and for 17 weeks thereafter.

7.8 Study Discontinuation and Study Withdrawal

7.8.1 Study Discontinuation (Early Termination)

Patients who discontinue treatment with tildrakizumab (Ilumetri®) prior to the regular end of the observation period, i.e., prior to Visit 9 should undergo an Early Termination Visit (see Table 5-1) as soon as possible after the decision for treatment discontinuation was made. Thereafter, the documentation in context with this NIS will be stopped.

Patients may withdraw their consent to participate in this NIS at any time at their own request and without giving reasons, without this having any adverse effect on their further treatment. If a participant withdraws his/her participation, the study physician is obliged to ask the participant about the further usability of his/her data (without restriction, anonymization or deletion) and to document his/her decision.

If the study physician decides to withdraw the patient from treatment with tildrakizumab (Ilumetri®), he will be asked to document the date and reason for his decision. Additionally, he will be asked to indicate the new therapy.

The patients will be advised that participation in this NIS is voluntary. Patients will not be compensated for participating in this NIS. Furthermore, the patients may request that no more data will be recorded from the time point of the ICF withdrawal.

In case of premature discontinuation, the assessments scheduled for the Early Termination Visit examination will be performed as soon as possible.

7.9 Investigational Medicinal Product, Dosage and Mode of Administration

Substance 1 code/name: Tildrakizumab (Illumetri®)

Administration route: subcutaneous

Unit dose/strength: 100 mg/200 mg

Dose form: Pre-filled syringe with 1ml injectable solution containing 100 mg of tildrakizumab.

Frequency: For newly tildrakizumab (Ilumetri®) prescribed patients the recommended dose should be administered by subcutaneous injection at Week 0/Day 0, Week 4 and every 12 weeks thereafter. For patients who completed clinical trials with tildrakizumab (Ilumetri®) no induction period is needed. These patients may continue administration of tildrakizumab (Ilumetri®) every 12 weeks as indicated in the SmPC.

Mode of administration: Ilumetri® is administered by subcutaneous injection. Injection sites should be alternated. Ilumetri® should not be injected into areas where the skin is affected by plaque psoriasis or is tender, bruised, red, hard, thick, or scaly. The pre-filled syringe must not be shaken. Each pre-filled syringe is for single use only.

The full amount of tildrakizumab (Ilumetri®) will have to be injected according to the instructions for use provided in the package leaflet.

After a proper training in subcutaneous injection technique, patients may self-inject Ilumetri® if a study physician determines that it is appropriate. However, the study physician should ensure appropriate follow-up of patients. Patients should be instructed to inject the full amount of Ilumetri® according to the instructions provided in the package leaflet. Comprehensive instructions for administration are given in the package leaflet.

8 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

8.1 Definition of Adverse Events/Adverse Drug Reactions

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

A Serious Adverse Event (SAE) is any experience that suggests a signification hazard, contraindication, side effect or precaution. With respect to human clinical experience, this includes any event which:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
- results in persistent of significant disability / incapacity, or
- is a congenital anomaly / birth defect,
- is a significant or important medical event that, based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

An ADR is an injury caused by taking medication. ADRs may occur following a single dose or prolonged administration of a medicinal product or result from the combination of two or more medicinal products. An ADR is a special type of AE in which a causative relationship to the medicinal product can be shown.

8.2 Documentation and Reporting of Adverse Drug Reactions, Events with Fatal Outcome and Other Reportable Events

Each ADR for which a causal relationship to tildrakizumab (Ilumetri®) cannot be excluded, must be comprehensively documented on the "Adverse Drug Reaction" form and be reported within 1 working day (24 hours) of learning of the event and be proactively reported to QPS Safety Group:

Email: safetySAIL@qps.com

In addition, all events with a fatal outcome and all other reportable events (lack of effectiveness of Ilumetri®, pregnancy, overdose, off-label use, misuse, abuse, medication error or occupational exposure) – even in the absence of an ADR – must be documented on the "Adverse Drug Reaction" form and be reported to QPS Safety Group within 1 working day (24 hours) of learning of the event (see above).

Early terminated (ET) patients as well as patients who completed EOS visit will be evaluated for safety assessments at approximately 12 weeks after the last injection of tildrakizumab. This will be documented in the eCRF.

QPS Austria Safety Group will forward these reports to the Drug Safety Department of Almirall S.A. in Spain as defined in an appropriate safety management plan.

8.3 Documentation of other, non-fatal SAEs

Non-serious ADRs have to be reported within 3 business days via the ADR report form. Other, non-fatal, SAEs will be recorded in the eCRF **only**.

9 STATISTICAL METHODOLOGY AND ANALYSES

9.1 Statistical Analyses

Statistical analyses are performed using the SAS program system.

According to the non-interventional character of the study, the statistical analysis is descriptive and explorative. No statistical hypotheses are formulated. A detailed statistical analysis plan (SAP) will be written before the analysis.

Descriptive summary statistics will be provided for all effectiveness endpoints over time based on observed data (without imputation for missing data). Multiple Imputation analysis will be conducted as a sensitivity analysis. These analyses will be based on FAS population.

For safety, number and percentage of patients with any Adverse Event will be provided. These analyses will be based on Safety Population.

9.1.1 Statistical Analyses Populations:

There will be two analyses populations in this trial:

- Full Analyses Set (FAS), defined as all those patients in safety population that had at least some effectiveness data.
- Safety population, defined as all patients for whom it is known that they had at least one tildrakizumab dose during the study duration.

9.1.2 Interim analyses

An interim analysis will be performed after 150 patients completed Visit 5.

9.1.3 Sample Size

The maximum total number of patients to be included in this study will be 430. The patients will be assigned to one of the following cohorts:

- Cohort 1: patients who completed tildrakizumab clinical trials
- Cohort 2: newly tildrakizumab prescribed patients

Patients meeting all of inclusion and none of exclusion criteria may be included in the study in every participating site.

Due to the exploratory nature of this study, this maximum number of patients has been considered enough to meet the objectives of the study.

9.2 Safety and Tolerability Parameters

An adverse drug reaction (ADR) is defined as:

“Adverse drug reactions to medicinal products intended for human use are harmful and unintended reactions to the medicinal product.”

A serious ADR is a reaction, which:

- Results in death,
- Is life-threatening,
- Requires hospitalization or prolongation of existing inpatients’ hospitalization,
- Results in persistent or significant disability or incapacity,

- Results in a congenital anomaly or birth defect
- Is a medically important event.

A medically important event is defined as an event that endangers the patient and may require medical or surgical intervention to prevent a serious adverse event.

ADRs must be temporally associated with the patient's participation in the study, i.e., occur between signing the informed consent and the last scheduled contact with the patient.

The severity of an ADR, whether serious or not, is assessed according to the following definitions:

- Mild: Awareness of sign, symptom, or event, but easily tolerated;
- Moderate: Discomfort enough to cause interference with usual activity and may warrant intervention;
- Severe: Incapacitating with inability to do normal daily living activities or significantly affects clinical status, and warrants intervention;

The safety set will be used to perform all safety analyses.

The medical history will be coded using the MedDRA Version 22.0 or newer and listed.

The ADRs and AEs are tabulated by system organ class (SOC), and individual preferred terms within each SOC by treatment group (100 mg or 200 mg tildrakizumab). The number and percentage of patients who experienced AEs coded with the same preferred term and SOC will be summarized by treatment group (in descending order according to the incidence in the investigational study drug group). ADRs and AEs will also be tabulated by severity and by relationship to study drug. Summary tables will be accompanied by individual patient listings broken down by treatment group, including pre-dose events.

SAEs will be listed and summarized similarly to AEs.

All AEs and SAEs are coded using the MedDRA Version 22.0.

Reasons for death will only be listed.

9.3 Baseline Parameters and Concomitant Medications

Summary statistics (mean, median, standard deviation, min, max, number of available observations) will be provided for continuous demographic variables (e.g. age, gender). Individual patient listings of demographic data will be provided.

Qualitative demographic characteristics (gender) will be summarized by counts and percentages. Other baseline patient characteristics (medical history, physical examination clinical findings, previous medications, inclusion/exclusion checklist) will only be listed.

Distributions of these parameters will be compared between the treatment groups (100 mg or 200 mg tildrakizumab) only descriptively. No statistical inference will be performed.

Previous and concomitant medications will be coded by the sponsor according to the WHO drug code and the ATC class code. Previous medications will be summarized by tabulating the number and percentages of patients treated.

9.4 Exploratory Analyses

Exploratory data-driven analyses can be performed with the caveat that any statistical inference will not have any confirmatory value.

9.5 Effectiveness Parameters

Baseline is defined as the last value measured on Day 0 (Week 0) prior to the first tildrakizumab (Ilumetri) administration (also if patients participated in tildrakizumab (Ilumetri®) clinical trials).

The following primary effectiveness parameters have been defined for Cohort 1:

Cohort 1 (Subgroup of patients continuing treatment with tildrakizumab):

- Absolute PASI scores and change from baseline value at Visit 5 and Visit 9 (EOS)
- Correlation between absolute PASI scores and DLQI-R at Visit 5 and Visit 9 (EOS)
- Percentage of patients maintaining PASI 75, 90, 100 responses at Visit 5 and Visit 9 (EOS) (re-SURFACE studies (if available) and Week 0/Day 0 of SAIL study)
- Absolute BSA and change of BSA from baselines (reSURFACE and SAIL) at Visit 5 and Visit 9 (EOS)
- Absolute PGA (general, nail, scalp) and change from baseline values (reSURFACE and SAIL) at Visit 5 and Visit 9 (EOS)

Cohort 2 (Newly prescribed patients):

- Absolute PASI scores and change from baseline value at Visit 5 and Visit 9 (EOS)
- Correlation between absolute PASI scores and DLQI-R at Visit 5 and Visit 9 (EOS)
- Percentage of patients achieving PASI 75, 90, 100 at Visit 5 and Visit 9 (EOS)
- Absolute BSA and change from baseline value at Visit 5 and Visit 9 (EOS)
- Absolute PGA (general, nail, scalp) and change from baseline value at Visit 5 and Visit 9 (EOS)

The following secondary effectiveness parameters have been defined:

- Absolute DLQI and DLQI-R score and change from baseline value at Visit 5 and Visit 9 (EOS) (both baselines for continuing patients if data available)
- Absolute VAS (patient and physician´s satisfaction with therapy, pain and itch) scores and change from baseline (both baselines for continuing patients if data available)
- Proportion of patients adding concomitant medications from baseline at Visit 5 and Visit 9 (EOS)
- Changes in weight measurements (body weight, BMI, waist and hip circumference (optional), waist/hip ratio (optional)) and blood pressure from baseline at Visit 9 (EOS) or Early Termination
- Changes in food intake: quantitative and qualitative from baseline up to Visit 9 (EOS) or Early Termination.
- Changes in physical activity: quantitative and qualitative from baseline up Visit 9 (EOS).
- Changes in lipid blood parameters in patients from baseline up to Visit 9 (EOS), if routinely available.
- Number and proportion of patients withdrawing from the study.

- Number of patients changing the dose (if any) and factors that influence the study physician's decision regarding the prescription of a dose of tildrakizumab (100 mg or 200 mg, if appropriate) (option based scale)
- Drug survival up to Visit 9 (EOS)
- Patient adherence up to Visit 9 (EOS)

9.5.1 Effectiveness Statistical Analysis

Descriptive summary statistics will be provided for all effectiveness endpoints over time based on observed data (without imputation for missing data). Multiple Imputation analysis will be conducted as a sensitivity analysis. These analyses will be based on FAS population.

9.6 Clinical Study Report

Study results will be included the study report that will be submitted to the Competent Authorities and ECs, if applicable, for publication according to national law and regulations.

10 PROCEDURES

10.1 Procedures

10.1.1 Protocol Amendments

Any substantial change to a protocol has to be considered as an amendment as soon as these documents have been submitted to ECs/IRBs or Health Authorities. Therefore, an amendment could occur before or after the approval of these documents by ECs/IRBs or Health Authorities. Each amendment must be documented in writing and approved by Almirall.

Adaptations of the core Patient Information and Informed Consent requested by ECs/IRBs are not considered as amendments, as long as they do not significantly change the core document or affect the protocol.

10.1.2 Monitoring

The study Clinical Research Organization (CRO) QPS Austria GmbH has been designated by the sponsor to monitor the study progression. An initiation visit will be performed before the first patient is included to explain the study and instruct on the completion of the eCRF.

During the study, the monitor will be the primary contact person in case of questions regarding documentation of data, query resolution, etc. To improve data quality, remote monitoring is planned as a risk-based approach.

At the end of the study, each participating site will be remotely closed by the monitor.

The study physician must ensure that patients' anonymity will be maintained. On eCRFs or other documents submitted to Almirall, patients should not be identified by their names, but by the patient number. The study physician must keep a patient identification code list showing the identification number, the patient's name, date of birth and address or any other locally accepted identifiers. Documents identifying the patients (e.g., patients' signed informed consent forms) should not be sent to Almirall and must be kept by the study physician in strict confidence.

The study physician and his/her deputy agree to cooperate with the monitor(s) to ensure that any issue detected is resolved. If the patient is hospitalized or dies in a hospital other than the study center, the study physician is in charge of contacting this hospital in order to document this SAE.

The study physician will supply Almirall on request with any required background data from the study documentation or clinic records. This is particularly important when eCRFs are illegible or when errors in data transcription are suspected. In case of special problems and/or governmental queries, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

10.1.3 Data Management

10.1.3.1 Data Collection

The data will be captured on an electronic CRF (eCRF). The data management will be conducted by QPS with relevant standards and procedures to ensure data integrity, e.g., eliminating errors and inconsistencies in the data, as well as data authenticity and confidentiality. All quality control activities will be described in the data validation plan.

All medications will be coded using the drug dictionary of the World Health Organization (WHO-DD). All ADRs/deaths/other reportable events and medical histories will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

If a patient withdraws from the study, the reason must be noted on the eCRF. Case report forms are to be completed on an ongoing basis.

Designated study physician staff will enter the data required by the protocol into the electronic Case Report Forms. Designated study physician site staff will not be given access to the EDC system until they have been trained. The study Physician must certify that the data entered into the eCRFs are complete and accurate.

10.1.3.2 Database Management and Quality Control

All data from the source documents will be entered into the eCRF. After completion of the eCRF, each patient will be electronically approved (signed) by the physician.

The CRA will use the eCRF system to track the monitoring queries and their resolution by the site.

The entered data is systematically checked by Data Management according to the data validation plan and the applicable SOPs.

After the eCRF has been declared complete and accurate, the eCRF will be locked, after written approval of the sponsor. Any changes to the eCRF after that time can only be made after receipt of written approval of the sponsor.

10.1.4 Audit

The Almirall Quality Management Department may conduct audits of clinical research activities in accordance with internal standard operating procedures (SOPs) to ensure that the clinical study is performed and data are generated, documented (recorded) and reported in compliance with the applicable regulatory requirements..

Health Authorities may also wish to conduct an inspection (during the study or after its completion). Should an inspection be requested by Health Authorities, the study physician must inform Almirall immediately that such request has been made.

The study physician will permit such audits by Almirall or Health Authorities and facilitate them by providing access to the relevant source documents.

10.1.5 Publication of Study Results

In accordance with standard editorial and ethical practice, Almirall will support publication of the data. This will be done under the responsibility of Almirall.

10.2 Confidentiality of Data and Patient Protection

10.2.1 Confidentiality of Data

Personal data will be collected, stored and processed exclusively in pseudonymized form. The data will be processed in accordance with the European GDPR EU 2016/679 and national regulations.

The study physician's file will contain the signed protocol/amendments, site staff curriculum vitae and authorization forms, signed conflict of Interest forms, eCRFs and data clarification and query forms, Health Authority and EC approval, if applicable, and signed informed consent

forms. The study physician file will be updated by the site accordingly. The study physician will ensure that this study is conducted in full conformance with the laws and regulations of the country in which the NIS is conducted.

10.2.2 Ethics Committee / Institutional Review Board

The study physician will submit this protocol and any related document provided to the patient (such as patient information used to obtain informed consent) to an Ethics Committee (EC) or Institutional Review Board (IRB). Approval from the committee must be obtained before starting the study, and should be documented in a dated letter to the study physician, clearly identifying the study, the documents reviewed and the date of approval. The advice of the ethics committee is intended to ensure that the rights of the patients participating in this study are not impaired and that the NIS is designed to gain knowledge.

10.2.3 Informed Consent

The Informed Consent and Patient Information will be provided in the local language.

With regard to therapy decisions, the patient does not need to be informed beyond the usual professional duty of the study physician to provide information.
The patients will be informed about the collection and evaluation of data within the framework of the NIS as well as about their rights regarding the processing of their personal data according to the General Data Protection Regulation (GDPR) prior to participation and must give their written consent to participation.
The patient will receive a written version of the patient information and one of two originals of the dated and signed consent form. The study physician documents the patient's information and consent in the medical records.

11 RISK ANALYSIS

The Monitoring Plan will include a risk-based approach.

12 REFERENCES

1. Bangert C, Kopp T. Tildrakizumab for the treatment of psoriasis. Immunotherapy. septiembre de 2018;10(13):1105-22
2. Behzadi P, Behzadi E, Ranjbar R. IL-12 Family Cytokines: General Characteristics, Pathogenic Microorganisms, Receptors, and Signalling Pathways. *Acta Microbiol Immunol Hung* 2016; **63**: 1–25
3. Blauvelt A, Reich K, Papp KA, et al. Safety of tildrakizumab for moderate-to-severe plaque psoriasis: pooled analysis of three randomized controlled trials. Br J Dermatol. 2018;179(3): 615-622
4. Bremmer S, Van Voorhees AS, Hsu S, Korman NJ, Lebwohl MG, Young M, et al. Obesity and psoriasis: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol. 2010; 63(6):1058±69.
5. Cargill M, Schrodi SJ, Chang M, Garcia VE, Brandon R, Callis KP, et al. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. Am J Hum Genet. 2007;80(2):273–290
6. Choi SH, Chae A, Miller E, Messig M, Ntanios F, DeMaria AN, Nissen SE, Witztum JL, Tsimikas S. Relationship between biomarkers of oxidized low-density lipoprotein, statin therapy, quantitative coronary angiography, and atheroma: volume observations from the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) study. J Am Coll Cardiol. 2008;52:24–32.
7. U.S. National Library of Medicine [cited 05 June 2019]: https://clinicaltrials.gov/ct2/show/NCT01729754?term=tildrakizumab+phase+III&cond=psoriasis&rank=1
8. U.S. National Library of Medicine [cited 05 June 2019]: https://clinicaltrials.gov/ct2/show/NCT01722331?term=tildrakizumab+phase+III&cond=psoriasis&rank=2
9. European Medicines Agency. Summary of product characteristics: Ilumetri. 2018 [cited 05 June 2019]. https://www.ema.europa.eu/en/medicines/human/EPAR/ilumetri
10. Fernández-Armenteros JM, Gómez-Arbonés X, Buti-Soler M, Betriu-Bars A, Sanmartin-Novell V, Ortega-Bravo M, Martínez-Alonso M, Garí E, Portero-Otín M, Santamaria-Babi L, Casanova-Seuma JM. Psoriasis, metabolic syndrome and cardiovascular risk factors. A population-based study. J Eur Acad Dermatol Venereol. 2019 Jan;33(1):128-135
11. Gemeinsame Bekanntmachung des Bundesinstituts für Arzneimittel und Medizinprodukte und des Paul-Ehrlich-Instituts zur Anzeige von Anwendungsbeobachtungen nach § 67 Absatz 6 Arzneimittelgesetz. Entwurffassung vom 20. Oktober 2014.
12. Nair RP, Duffin KC, Helms C, Ding J, Stuart PE, Goldgar D, et al. Genome-wide scan reveals association of psoriasis with IL-23 and NF-κB pathways. Nat Genet. febrero de 2009;41(2):199-204
13. Oppmann B, Lesley R, Blom B, Timans JC, Xu Y, Hunte B *et al.* Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. *Immunity* 2000; **13**: 715–725.
14. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and resurface 2): results from two randomised controlled, phase 3 trials. Lancet. 2017;390(10091):276-88
15. Rencz F, Gulácsi L, Péntek M, Poór AK, Sárdy M, Remenyik E, Brodszky V, Proposal of a new scoring formula for the Dermatlology Life Quality Index in psoriasis. Br J Dermatol. 2018 Nov; 179(5):1102-1108. doi: 10.1111/bjd.16927. Epub 2018 Sep 19.

16. Sinclair R, Thirthar Palanivelu V. Tildrakizumab for the treatment of psoriasis. Expert Rev Clin Immunol. 3 de noviembre de 2018;1-8
17. Thaçi D, Iversen L, Pau-Charles I, Rozzo S, Blauvelt A, Reich K. Long-term efficacy and safety of tildrakizumab in patients with moderate-to-severe psoriasis who were responders at week 28: pooled analysis through 3 years (148 weeks) from reSURFACE 1 and reSURFACE 2 phase 3 trials. EADV 2018
18. Tang C, Chen S, Qian H, Huang W. Interleukin-23: as a drug target for autoimmune inflammatory diseases. *Immunology* 2012; **135**: 112–124.
19. TSQM Version 1.4: Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes. 2004;2:12. Those seeking information regarding or permission to use the TSQM are directed to IQVIA at www.iqvia.com/TSQM or TSQM@iqvia.com
20. Warnick GR, Knopp RH, Fitzpatrick V, Branson L. Estimating lowdensity lipoprotein cholesterol by the Friedewald equation is adequate for classifying patients on the basis of nationally recommended cutpoints. Clin Chem. 1995;36(1):15–19.
21. Wilson NJ, Boniface K, Chan JR, McKenzie BS, Blumenschein WM, Mattson JD *et al.* Development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nat Immunol* 2007; **8**: 950–957.