

NON-INTERVENTIONAL STUDY PROTOCOL
**Efficacy and flexibility of Tildrakizumab
treatment in patients with moderate-to-severe
plaque psoriasis and high disease burden
Acronym: TILFLEX**

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Efficacité et flexibilité du traitement par Tildrakizumab chez des patients atteints de psoriasis en plaques modéré à sévère et présentant un fardeau élevé de la maladie

Principal Investigator

I, the undersigned, have read and understood this protocol v1.0 dated 18/09/2024. I am aware of my responsibilities and I accept the following provisions:

- To conduct this clinical study in accordance with the design and specific terms of this protocol;
- To apply Good Clinical Practices (GCP), the Declaration of Helsinki, and all other regulatory requirements;
- To comply with the data registration and communication procedures;
- To allow monitoring, auditing, and inspection by the CRO, the Sponsor, and the relevant regulatory authorities;
- To retain study-related documents in compliance with regulatory requirements and as agreed with the Sponsor;
- To handle all information related to the study confidentially.

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Signature of the investigator:

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2. ABBREVIATIONS

Abréviations	Définitions
AE	Adverse Event
ADR	Adverse Drug Reaction
AMM	Autorisation de mise sur le marché (Marketing authorisation)
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé (French National Agency for Medicines and Health Products Safety)
BMI	Body Mass Index
BS	Body Surface Area
CI	Confidence Interval
CKD	Chronic Kidney Disease
CPP	Committee for the Protection of Persons
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CV	Cardiovascular
CVD	Cardiovascular Diseases
DLQI	Dermatology Life Quality Index
eCRF	electronic Case Report Form
ESRD	End-Stage Renal Disease
f-PGA	Finger nail Physician Global Assessment
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HR	Hazard ratio
IL	Interleukin
MI	Myocardial Infraction
OR	Odds ratio
PASI	Psoriasis Area and Severity Index
PGA	Physician Global Assessment
PP-PGA	Palmoplantar Physician Global Assessment
PsA	Psoriasis Arthritique
PRO	Patient Reported Outcomes
SAE	Serious Adverse Event
SADR	Serious Adverse Drug Reaction indésirable grave lié au médicament
SmPC	Summary of Product Characteristics
sPGA-G	Static Physician Global Assessment of Genitalia
RIHP	Research Involving Human Person

3. SUMMARY

3.1 Synopsis

STUDY TITLE	Efficacy and flexibility of treatment by Tildrakizumab in patients with moderate-to-severe plaque psoriasis with high disease burden.
ACRONYM	TILFLEX
SPONSOR	ALMIRALL
RATIONAL	<p>Psoriasis is a chronic inflammatory disease that affects 125 million people around the world with major repercussions on physical and emotional quality of life of patients.</p> <p>Many studies confirmed the association between psoriasis and comorbidities as cardio vascular diseases, gastrointestinal, kidney diseases, cancers, infections or mood disorders. Psoriasis, specially, when it is severe, is associated with highest mortality and a disease burden linked to comorbidities. Understanding this disease burden associated to psoriasis is crucial for an optimal medical care.</p> <p>Tildrakizumab is indicated in treatment of moderate-to-severe plaque psoriasis in adults who need a systemic treatment, also, in case of failure, intolerance or contraindication to a systemic treatment, including Methotrexate. Tildrakizumab 200mg has already shown its long-term efficacy in treatment of psoriasis and safety in clinical trials and retrospective studies in patients with a high disease burden or body weight ≥ 90 kg. Further prospective investigations in real-life are required to confirm the efficacy of Tildrakizumab 200mg in patients with psoriasis and high disease burden (comorbidities, difficult-to-treat locations, severe form of psoriasis, treatment failure...).</p>
OBJECTIVE OF THE STUDY	<p>To evaluate the efficacy, safety and flexibility of Tildrakizumab in patients with moderate-to-severe plaque psoriasis with disease burden and/or body weight ≥ 90Kg.</p> <p>The primary objective is to evaluate the efficacy of Tildrakizumab 200mg at week (W)28.</p> <p>Secondary objectives are:</p> <p>1/ Evaluate the maintain of efficacy of Tildrakizumab at W52 and W76.</p> <p>2/ Evaluate the maintenance of efficacy of Tildrakizumab in case of dose reduction of Tildrakizumab by dermatologist (from</p>

	<p>Tildrakizumab 200 mg to Tildrakizumab 100mg).</p> <p>3/ To study the quality of life and general well-being and their evolution while treatment.</p> <p>4/ To study the safety of Tildrakizumab and occurrence of adverse events throughout follow-up.</p> <p>Exploratory objectives are:</p> <p>1/ To study and describe contributing elements to disease burden in real-life.</p> <p>2/ Identify participants profiles according to rapidity of response to treatment, its maintenance throughout follow-up and contributing elements to disease burden identified.</p> <p>3/ Identify the delay and associated conditions to dose change of Tildrakizumab.</p>
ASSESSMENT CRITERIA	<p>Main criteria: The response to Tildrakizumab will be assessed by « PASI absolute (Psoriasis Area and Severity Index) » at W28.</p> <p>Secondary and Exploratory endpoints:</p> <ul style="list-style-type: none"> - Maintenance of treatment response will be assessed by PASI absolu at W52 and W76 according to Tildrakizumab dose (200mg or 100mg). <p>NB: For patients who present difficult-to-treat sites, global response will be adjusted on specific response assessed by this (these) difficult-to treat locations scores based on specific score equal to 0 or 1 or decrease of at least 2 points from Baseline visit.</p> <p><i>For nail: finger nail PGA (f-PGA)</i> <i>For scalp: Scalp PGA</i> <i>For palmoplantar: palmoplantar PGA (PP-PGA)</i> <i>For genital: static Physician's Global Assessment of Genitalia (sPGA-G)</i></p> <ul style="list-style-type: none"> - Quality of life will be estimated from Dermatology quality of life DLQI (french version). - Wellbeing will be estimated from the questionnaire WHO-5 (french version) - Treatment compliance will be assessed by an self-administrated questionnaire.
SCHEMA D'ETUDE	<p>Observational, prospective, multicenter, national postmarketing follow-up study.</p> <p>Terms of inclusion:</p> <ul style="list-style-type: none"> - Inclusion of patients (age ≥ 18 years) with prior indication to initiate

	<p>treatment with Tildrakizumab 200mg without change in management strategy.</p> <ul style="list-style-type: none"> - Consecutive recruitment (study offered to all eligible patients) - Strict identification of eligible patients not included - Competitive recruitment between participating sites <p>Conduct of the study: Site visits at Baseline (W0), W28, W52 and W76.</p> <p>Baseline visit (W0): Provision of information and collection of non-opposition (trace the modalities of information and collection of non-opposition in the patient's file)</p> <ul style="list-style-type: none"> - Collection of the following information (if not available in the medical record) : <ul style="list-style-type: none"> Age, gender Family history Personal history Lifestyle Characterisation of psoriasis Previous treatments for psoriasis Ongoing treatments of psoriasis Comorbidities - Perform a clinical examination (including weight and height) - Verification of the absence of serious progressive infection contraindicating the use of Tildrakizumab (according to standard care) - Verification of the absence of pregnancy for women of childbearing age (according to standard care) - Global psoriasis evaluation: identification of psoriasis locations, PASI and PGA, functional signs. - For participants with difficult-to-treat locations, evaluation using the following specific scores: <ul style="list-style-type: none"> • For the nail: finger nail PGA (f-PGA) • For the scalp: scalp PGA • For the palmoplantar: palmoplantar PGA (PP-PGA) • For genitalia: Static Physician's Global Assessment of Genitalia (sPGA-G) - DLQI, WHO-5, Physical activity assessment (Self-administred questionnaires). - Prescription of Tildrakizumab (according to AMM). <p><i>NB: Treatment should be initiated at week 0 (Baseline) at the latest within 4 weeks post visit and then at week 4 and every 12 weeks thereafter according to the PCR. The initial dosage or dose adjustment during treatment is at the discretion of the investigator.</i></p>
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W28 visit (+/- 4 weeks):

- Perform a clinical examination (with weight collection)
- Collection of adverse events (AEs)
- Collection of ongoing psoriasis treatments
- Assessment of comorbidities
- Global psoriasis evaluation: PASI, PGA, functional signs.
- For patients with difficult-to-treat locations, evaluation using the following specific scores:
 - For the nail: finger nail PGA (f-PGA)
 - For the scalp: scalp PGA
 - For the palmoplantar: palmoplantar PGA (PP-PGA)
 - For genitalia: Static Physician's Global Assessment of Genitalia (sPGA-G)
- Tildrakizumab dose re-evaluation
- DLQI, WHO-5, Compliance (self-administreted)

W52 visit (+/- 4 weeks):

- Perform a clinical examination (with weight collection)
- Collection of adverse events (AEs)
- Collection of ongoing psoriasis treatments
- Assessment of comorbidities
- Assessment of psoriasis: PASI, PGA, functional signs.
- For patients with difficult-to-treat locations, evaluation of sites using the following specific scores:
 - For the nail: finger nail PGA (f-PGA)
 - For the scalp: scalp PGA
 - For the palmoplantar: palmoplantar PGA (PP-PGA)
 - For genitalia: Static Physician's Global Assessment of Genitalia (sPGA-G)
- Tildrakizumab dose re-evaluation
- DLQI, WHO-5, Compliance (self-administrated)

W76 visit (+/- 4 weeks):

- Perform a clinical examination (with weight collection)
- Collection of adverse events (AEs)
- Collection of lifestyle
- Collection of ongoing psoriasis treatments
- Assessment of comorbidities
- Global psoriasis evaluation: PASI, PGA, functional signs.
- For patients with difficult-to-treat locations, evaluation using the following specific scores:
 - For the nail: finger nail PGA (f-PGA)
 - For the scalp: scalp PGA
 - For the palmoplantar: palmoplantar PGA (PP-PGA)
 - For genitalia: Static Physician's Global Assessment of Genitalia (sPGA-G)
- Tildrakizumab dose re-evaluation
- DLQI, WHO-5, Compliance, physical activity assessment (self-

	<p>administreted)</p> <p>NB: If the participant stops his treatment by Tildrakizumab, the investigator will record in the CRF:</p> <ul style="list-style-type: none"> - Reason for discontinuation - New line of treatment if applicable <p>Data processing and quality control:</p> <p>Data from each visit will be collected in a paper CRF (CRFp). One copy will be kept on site.</p> <p>Data entry from the pCRFs will be centralized and duplicated in a digital solution hosted on servers in Europe that are approved as a Health Data Host (HDS), in compliance with Good Clinical Practice and MR003.</p> <p>Data quality will be assessed through data consistency checks, descriptive statistical review of the data, and source data monitoring. The percentage of monitoring of key data from the source file will be adapted to the risks of the study and adjusted on performance indicators measured throughout the study and defined according to a monitoring plan established before the beginning of the study.</p>
<p>STUDY POPULATION ELIGIBILITY CRITERIA</p>	<p>Inclusion criteria</p> <ol style="list-style-type: none"> 1. Patient with a diagnosis of moderate to severe chronic plaque psoriasis documented in the medical record, defined by: <ul style="list-style-type: none"> PASI $\geq$ 10 And/or body surface area (BS) affected $\geq$ 10% And/or DLQI $\geq$ 10 2. Disease diagnosis > 6 months (regardless of severity at diagnosis) 3. Body weight $\geq$ 90kg and/or a high burden of disease (assessed by physician) 4. Indication for treatment with an IL-23 inhibitor. Tildrakizumab 200mg must be the selected anti-IL-23 therapy prior to enrolling the patient in the study. 5. Patient 18 years of age or older at the inclusion visit 6. French social security affiliation/entitlement <p>Critères de non-inclusion</p> <ol style="list-style-type: none"> 1. Patient unable to comply with study requirements (complete study questionnaires) 2. Patient who, in the opinion of the investigator, should not participate in the study. This opinion should be documented in the patient's record. 3. Patient included in an interventional clinical trial at inclusion. Except in exceptional cases, concurrent participation in an interventional clinical trial will not be possible during the course of the study and must be discussed in advance with the Sponsor. 4. Vulnerable patient or patient under court protection

	<ol style="list-style-type: none"> 5. Patients with known hypersensitivity to IL-23 inhibitors 6. Patients with active HIV, HBV or HCV infection at the time of inclusion 7. Patient with a history of untreated latent tuberculosis or active tuberculosis at inclusion 8. Patient with any other serious active infection* present at inclusion that contraindicates anti-IL23 use. 9. Pregnant or lactating patients at baseline. Patients of childbearing potential will be informed of the need to use effective contraception during treatment**. <p><i>* In accordance with the Tildrakizumab Product Monographs, the investigator should ensure the absence of serious progressive infection throughout the follow-up.</i></p> <p><i>**In accordance with the Tildrakizumab Product Monograph, the investigator must ensure the absence of pregnancy throughout follow-up and the use of an effective method of contraception during treatment with Ilumetri and for at least 17 weeks after treatment.</i></p>
<p>STATISTICAL METHODOLOGY</p>	<p>Statistical analysis</p> <p>Main analysis: The percentage of response of absolute PASI categorized at W28 will be estimated and its 95% confidence interval.</p> <p>Secondary analysis:</p> <p>As the study is primarily descriptive, continuous and discrete variables will be summarized using descriptive statistics (number of observations, mean, standard deviation, median, interquartile range (Q1, Q3), range (mode)). Categorical variables will be summarized by their frequency.</p> <p>All tests of statistical significance will be two-sided at 95%. The risk of error for statistical tests will be set at 5% in two-tailed.</p> <p>Percentage response will be described in terms of absolute PASI categorized by subgroups based on criteria of interest (difficult-to-treat sites, Body Mass Index (BMI) categories, severity of psoriasis, etc.).</p> <p>The evolution of mean PASI scores between inclusion and the various visits will be studied using analysis of variance (mixed ANOVA for repeated measures followed by comparison of means using the least-squares method) to take into account the dose of Tildrakizumab used (100mg or 200mg) and compliance with treatment.</p> <p>Disease burden will be described on the basis of comorbidities and patient history, previous psoriasis therapy failures, disease severity, polymedication and functional signs.</p> <p>For the efficacy maintenance, temporal analyses and Sankey plot graphs will be used to confirm the best model to use.</p> <p>For the other secondary endpoints, parameters will be described and compared at each period.</p> <p>The global quality of life score DLQI and the WHO-5 well-being questionnaire will be described at visits S0, S28, S52 and S76.</p>

	<p>Patient profiles according to response will be determined on the basis of maintenance of absolute PASI at visits S52 and S76 respectively, taking into account dosage change. Patient profiles according to response and disease burden will be explored using multinomial logistic regression models and/or machine learning algorithms such as <i>random forest</i> or <i>confidence inference trees</i>.</p> <p>Methods to limit selection bias:</p> <ul style="list-style-type: none"> - Non-selective consecutive recruitment - Rigorous anonymous collection of eligible patients not included (age, sex, reason for non-inclusion). - Comparison of study population characteristics with literature data. - Contact with potential lost to follow-up participants and consultation of the national death database by the centers if necessary. <p>Sample size</p> <p>Because the study was primarily descriptive, the population size was estimated:</p> <ul style="list-style-type: none"> - from the prevalence of psoriasis with a high burden of disease with indication of systemic treatment - and the capacity of hospitals to include these patients. <p>It is planned to include 120 patients.</p>
REGULATORY ISSUES	<p>Research study involving the human person mentioned in the 3° of the article L1121-1 of the public health code concerning a health product (product mentioned in the article L.5311-1 of the public health code) and including procedures other than questionnaires/interviews.</p> <p>As such, the study will be:</p> <ul style="list-style-type: none"> - submitted for opinion to a randomly selected Committee for the Protection of Persons (CPP) and the synopsis validated by the CPP will be transmitted to the ANSM for information. - Conduct according to Good Clinical Practices (GCP ICH E6 (R2)) <p>The sponsor undertakes to comply with the reference methodology MR-003 and the obligations defined by the General Data Protection Regulation (GDPR).</p> <p>The synopsis will be referenced in the clinicaltrials.gov public clinical trial registry prior to the start of the first inclusion.</p>
PHARMACOVIGILANCE	<p>In the context of this observational study, all adverse events and special situations will be collected throughout the follow-up period and reported in accordance with the current protocol.</p>
ESTIMATED DURATION OF THE STUDY	<p>Study start date (1st inclusion): Q4 2024</p> <p>Duration of inclusion: 10 months</p> <p>End of study (active phase excluding analyses - Last patient follow-up):</p>

	Q1 2027
PERIOD OF PARTICIPATION	76 weeks per participant
STUDY LOCATION/ INVESTIGATOR CENTERS	Study conducted in 25 to 30 clinical sites in France. Inclusion rate: 3 to 4 patients included per center over a 10-month period.
N° Version : 1.1 18 september 2024	

3.2 Summary of visits

	Baseline W0	Visit W28 (+/- 4 weeks)	Visit W52 (+/- 4 weeks)	Visit W76 (+/- 4 weeks)
Validation of eligibility criteria	X			
Providing information and collection of participant's non-opposition	X			
Collection of demographic data	X			
Collection of personal and family history personnels	X			
Collection of previous psoriasis treatments	X			
Lifestyle (smoking, alcohol, sedentary lifestyle)	X			X
Collection of ongoing psoriasis treatments	X	X	X	X
Collection of ongoing concomitant treatments	X			X
Characterization of psoriasis	X			
Assessment of comorbidities	X	X	X	X
Clinical exam with weight measurement (and height at W0 only)	X	X	X	X
General assessment of psoriasis: PASI, PGA, functional signs, specific ⁱ	X	X	X	X
Tildrakizumab 200 mg prescription	X			
Self-administred questionnaires : DLQI et WHO-5	X	X	X	X
Compliance questionnaire		X	X	X
Physical activity questionnaire	X			X
Collection of adverse events (AE)		X	X	X
Tildrakizumab dose reevaluation and prescription		X	X	X

ⁱ For patients with difficult-to-treat locations: nail : f-PGA, scalp : scalp PGA, palmoplantar : PP-PGA, genital : sPGA-G

3.3 Summary of study visits

Résumé des visites

	S0	S28	S52	S76
Patients characteristics	Sex Age Weight BMI ATCD Lifestyle Duration of psoriasis Comorbidities History of treatments and ongoing treatments for psoriasis Concomitant treatments	Weight Comorbidities Psoriasis Treatments	Weight Comorbidities Psoriasis Treatments	Weight Lifestyle Comorbidities Psoriasis Treatments Concomitant treatments
General clinical indicators	PASI PGA Functional signs DLQI WHO-5 Physical activity assessment	PASI PGA Functional signs DLQI WHO-5 Compliance Collection AE	PASI PGA Functional signs DLQI WHO-5 Compliance Collection AE	PASI PGA Functional signs DLQI WHO-5 Compliance Physical activity assessment Collection AE
Only if applicable :				
±Specific indicators deoending on psoriasis locations: nails, scalp, palmoplantar, genital	Nail finger PGA Scalp PGA PP-PGA sPGA-G	Nail finger PGA Scalp PGA PP-PGA sPGA-G	Nail finger PGA Scalp PGA PP-PGA sPGA-G	Nail finger PGA Scalp PGA PP-PGA sPGA-G

4. SCIENTIFIC RATIONALE

4.1 Epidemiology, pathogenesis and symptomatology of psoriasis

Psoriasis is a common chronic inflammatory disease affecting between 2% and 4% of the French population and around 125 million people worldwide ¹⁻³. Psoriasis has a significant impact on physical and emotional quality of life, comparable to that caused by other serious diseases ⁴⁻⁶. Epidemiological data, together with basic scientific research into the natural history and biology of psoriasis, have led to the recognition of this disease as a pathology with significant repercussions on health, going beyond skin involvement alone.

Severe psoriasis is associated with an increased risk of mortality, with cardiovascular causes being the most common⁷. Indeed, these patients have an elevated risk of cardiovascular death (HR 1.57; CI95% 1.26-1.96) compared to a population of patients without psoriasis. Further studies are needed to determine whether the increased mortality rate or excess mortality is due to psoriasis itself, treatments, behaviours or other factors ^{7,8}.

4.2 Comorbidities associated to psoriasis

Psoriasis, especially when severe, is associated with increased mortality ⁴⁻⁶ and comorbidity-related morbidity. Indeed, a growing number of studies in diverse populations and varied contexts underlie the existence of associations between psoriasis and cardiometabolic, gastrointestinal, renal pathologies, malignancies, infections and mood disorders. The pathogenesis of comorbidities in psoriasis patients remains unknown; however, it is hypothesized that common inflammatory pathways, similar cellular mediators, genetic susceptibility and shared risk factors may contribute.⁷

4.2.1 Cardiometabolic diseases

Cardiometabolic diseases are common in psoriasis patients, particularly in those with the most severe skin involvement ⁸.

Psoriasis may be an independent risk factor for diabetes and major adverse cardiovascular events, the risk being higher in patients with severe psoriasis.

-Cardiovascular diseases (CVD): In 2006, a large population-based cohort study in the UK, among subjects aged between 20 and 90, showed that psoriasis was associated with an increased risk of myocardial infarction (MI), regardless of traditional risk factors such as body mass index (BMI), smoking, hypertension, diabetes, gender and dyslipidemia⁸⁻¹⁰. Several meta-analyses investigating the risks of MI, stroke and cardiovascular (CV) mortality according to psoriasis severity, compared with subjects without psoriasis, had shown that patients with severe psoriasis had the highest cardiovascular risks than those with less severe forms. In a meta-analysis¹¹, severe psoriasis was associated with a significantly higher risk of cardiovascular mortality, with a relative risk (RR) of 1.39 (95% CI, 1.11 to 1.74), MI with an RR of 1.70 (95% CI, 1.32 to 2.18) and stroke with an RR of 1.56 (95% CI, 1.32 to 1.84). However, the CV risk persisted to a lesser extent in patients with mild psoriasis. These data suggest that psoriasis is associated with cardiovascular risk irrespective of disease severity. Long-standing psoriasis has also been identified to be associated with an increased risk of CVD¹¹⁻¹⁵.

Chronic systemic inflammation, particularly vascular inflammation, may be increased in psoriasis patients and contribute to atherogenesis¹⁶. Common pathophysiological pathways between psoriasis and CVD, including chronic inflammation mediated by type 1 (Th1) and Th17 T-helper cells, modulation of monocytes and neutrophils, increased oxidative stress, endothelial cell dysfunction, increased uric acid, angiogenesis and increased circulating microparticles may explain the increased risk of psoriasis-associated CVD^{7,17}.

Moreover, the persistent pathophysiological processes at the origin of psoriasis (epidermal hyperproliferation, inflammation and angiogenesis) may also exert pleiotropic adverse effects on the cardiovascular system, contributing to atherogenesis. Finally, the deregulation of common genes responsible for psoriasis, diabetes and CVD^{17,18} has been suggested.

- **Obesity:** Obesity is a known independent risk factor for psoriasis. The risk of psoriasis increases with BMI. A meta-analysis of 16 observational studies revealed a pooled Odds Ratio (OR) for the association between psoriasis and obesity of 1.66 (95% confidence interval [CI] 1.46-1.89). Among the studies in this meta-analysis that took psoriasis severity (defined by treatment regimens) into account, the pooled ORs for the association between obesity and mild and severe psoriasis were 1.46 (95% CI 1.17-1.82) and 2.23 (95% CI 1.63-3.05) respectively. It would also appear that there is a positive correlation between objective measures of psoriasis severity and obesity^{8,10,19,20}.

- **Hypertension:** is more common in psoriasis patients than in those without²¹. The risk of high blood pressure in these patients seems to increase with the degree of severity of the disease, with ORs found in a meta-analysis¹¹ around 1.30 (95% CI : 1,15-1,47) for mild psoriasis and 1.49 (95% CI: 1.20-1.86) for severe psoriasis, as defined by treatment regimens compared with control patients without psoriasis.²².

Moreover, the likelihood of poorly controlled hypertension appears to increase with the severity of psoriasis, regardless of BMI or other risk factors.^{8,10}.

- **Diabetes:** Psoriasis would be associated with an increased risk of diabetes, independently of traditional risk factors. A study of psoriasis patients showed a relative risk (RR) of diabetes of 1.27 (95% CI, 1.16-1.40). In this study, the risk of diabetes and the likelihood of insulin resistance and diabetic complications would increase with the severity of psoriasis, as defined by treatment regimens or affected body surface area, respectively, including after consideration of traditional risk factors such as BMI^{8,10,23}.

- **Dyslipidemia :** The prevalence of dyslipidemia appears to be higher in psoriasis patients, particularly in the absence of treatment¹⁷. A systematic review of 25 studies reported significant associations between psoriasis and dyslipidemia, with ORs ranging from 1.04 to 5.55, in most of the selected studies. The direction of the association between these two conditions remains ambiguous, as some studies suggest that dyslipidemia may be a risk factor for the development of psoriasis^{8,10,17}.

- **Metabolic syndrome:** Metabolic syndrome is generally defined by the presence of a combination of obesity, hypertension, insulin resistance and dyslipidemia. Metabolic syndrome and its individual components are more common in patients with psoriasis, with an estimated prevalence between 14.3 and 50%^{8,10,17,23}, in both adults and children²⁴. A meta-analysis of 12 observational studies found an OR of 2.26 (95% CI: 1.70-3.01) for the association between psoriasis and metabolic syndrome, although the analysis was limited by the presence of publication bias. In a cross-sectional study in the UK²⁰, the prevalence of metabolic syndrome was directly correlated with the body surface area affected by psoriasis^{8,10}.

4.2.2 Gastrointestinal disorders

Psoriasis may be associated with an increased incidence and prevalence of inflammatory bowel disease, particularly Crohn's disease²⁵.

Some studies suggest that psoriasis is associated with an increased prevalence of liver disease, particularly non-alcoholic fatty liver disease, especially when psoriasis is severe or there is an associated metabolic syndrome.^{10,17}

4.2.3 Nephropathies

In a large British cohort study of cause-specific mortality, patients with severe psoriasis were four times more likely to die from nephritis or non-hypertensive kidney disease than the general population²⁶. Severe psoriasis could be a risk factor for chronic kidney disease (CKD) and end-stage renal disease (ESRD), independent of traditional risk factors such as age, gender, BMI, CVD, diabetes, hypertension, dyslipidemia and nephrotoxic drugs (hazard ratio [HR] for CKD: 1.93, 95% CI 1.79-2.08, and HR for ESRD 4.15, 95% CI 1.70-10.11). However, as most studies were cross-sectional in nature, the direction of the association remains uncertain.

4.2.4 Malignant tumors

Psoriasis, particularly severe forms, may be associated with an increased risk of cancer²⁷. The risk of malignancy due to psoriasis itself remains uncertain. A study looking at causes of mortality showed that patients treated for severe psoriasis had a 41% increased risk of death from malignancy compared with those without psoriasis. A meta-analysis pooling the results of 112 observational studies assessing the risk of

malignancy in patients with psoriasis compared to patients without psoriasis suggests an increased risk of cancer with an RR of 1.21 (95% CI, 1.11-1.33)¹⁰. Increased risks of cancers of the upper aerodigestive tract, respiratory tract, liver, pancreas and urinary tract, as well as lymphoma, have also been suggested⁸. However, the level of heterogeneity between the included studies is high, making interpretation difficult. In addition, many studies failed to take into account important confounding factors.⁸

4.2.5 Mental health

Psoriasis has a major impact on patients' physical and emotional quality of life, comparable to that of other serious illnesses, which can predispose patients to the development of mood disorders such as depression, anxiety and suicidal thoughts. It has been suggested that mood disorders, particularly depression, are more common in psoriasis patients than in the general population (up to 62% higher prevalence). In a meta-analysis of 98 (mostly cross-sectional) studies investigating the association between psoriasis and depression, psoriasis patients had more depressive symptoms (pooled standardized mean difference 1.16; 95% CI 0.67-1.66) and were almost 1.6 times more likely to suffer from depression (pooled OR 1.57; 95% CI 1.40-1.76)²⁸.

The risk of depression in patients with psoriasis has been evaluated in numerous studies²⁹. In a UK cohort study, psoriasis was associated with an increased risk of depression (HR 1.39; 95% CI 1.37-1.41), anxiety (HR 1.31; 95% CI 1.29-1.34) and suicide risk (HR 1.44; 95% CI 1.32-1.57). The risk of depression was higher in patients receiving treatment for severe psoriasis (HR 1.72; 95% CI 1.57-1.88)⁸. Similarly, a cohort study of 50,000 US women without depression at baseline - part of the Nurses' Health Study - revealed that psoriasis was associated with an almost 30% increased risk of depression (HR 1.29; 95% CI 1.10-1.52) in women with psoriasis, independent of age, BMI, lifestyle factors and concomitant medical conditions³⁰.

4.2.6 Others notable pathologies

Other epidemiological studies have suggested associations between psoriasis and other emerging comorbid diseases, including chronic obstructive pulmonary disease³¹, peptic ulcer disease, sexual disorders and obstructive sleep apnea. Further research should enable us to better characterize known comorbidities and identify new associations of comorbid diseases with psoriasis.

comorbides émergentes, notamment la bronchopneumopathie chronique obstructive³¹, l'ulcère gastroduodénal, les troubles sexuels et l'apnée obstructive du sommeil. La poursuite des recherches devrait permettre de mieux caractériser les comorbidités connues et d'identifier de nouvelles associations de maladies comorbides avec le psoriasis.

Psoriatic arthritis (PsA): PsA is an inflammatory arthritis present in 6-42% of psoriasis patients. Approximately 15% of psoriasis patients have undiagnosed psoriatic arthritis. PsA appears to be more common in patients with more extensive or severe skin disease.³².

Eye diseases and psoriasis: Psoriasis was also associated with an increased risk of uveitis in patients with no history of ocular pathology in a retrospective study. Age over 60 and dry eye were associated risk factors. The risk of retinal damage was also higher¹⁰. A better understanding of the burden of disease associated with psoriasis is essential to ensure optimal medical management of patients.

4.3 Study rationale

Although a variety of biological agents are now available for the treatment of psoriasis, they differ in their rapid onset of action, long-term efficacy, safety profile and effects on comorbidities. Evidence of the long-term efficacy, flexibility of use and safety of the new drugs on comorbidities is relatively weak.^{33,34}.

Further investigations into the use of biotherapies, including Tildrakizumab, in patients with less common forms of psoriasis, systemic comorbidities or who have not responded to multiple biologic agents, are needed. These studies could help to better understand the full spectrum of Tildrakizumab's therapeutic potential.

TILFLEX study is a prospective phase IV study designed to assess the efficacy, safety and flexibility of use of Tildrakizumab in patients with moderate-to-severe plaque psoriasis associated with a high disease burden (existence of comorbidities, difficult-to-treat sites, disease severity, failure of previous treatment(s)).

This study should also enable us to assess the continued efficacy of Tildrakizumab and characterize its long-term safety profile in the treatment of psoriasis under real-life clinical conditions.

4.4 Tildrakizumab

4.4.1 Mechanism of action

IL-23 is a naturally produced cytokine involved in inflammatory and immune responses contributing to the pathogenesis of psoriasis.³⁵

Tildrakizumab is a humanized IgG1/k class monoclonal antibody produced in Chinese hamster ovary cells by the recombinant DNA technique, which binds specifically to the p19 protein subunit of the cytokine interleukin-23 (IL-23), without binding to IL-12, thus inhibiting its interaction with the IL-23 receptor and inhibiting the release of pro-inflammatory cytokines and chemokines involved in psoriasis formation^{36–38}.

4.4.2 Pharmacokinetic properties

Absorption

The subcutaneous formulation of Tildrakizumab demonstrated an absolute bioavailability ranging from 73% (90% CI: 46% - 115%, 200 mg subcutaneously vs 3 mg/kg intravenously) to 80% (90% CI: 62% - 103%, 50 mg subcutaneously vs 0.5 mg/kg intravenously) in healthy subjects, following a single-dose crossover comparison study. The maximum concentration (C_{max}) was reached 6.2 days after the injection. Population pharmacokinetic analysis revealed a 31% higher bioavailability in healthy subjects compared to patients with plaque psoriasis.

At steady state, following the administration of 100 mg of Tildrakizumab in patients with moderate to severe plaque psoriasis, the geometric means (% CV) for the values of AUC_{0-τ} and C_{max} were 305 µg.day/mL (41%) and 8.1 µg/mL (34%), respectively. After administration of 200 mg of Tildrakizumab, these values were 612 µg.day/mL (40%) and 16.3 µg/mL (33%), respectively.

Distribution

Tildrakizumab has limited extravascular distribution, with volume of distribution (Vd) values ranging from 76.9 to 106 mL/kg.

Biotransformation

Tildrakizumab is catabolized into amino acids through general protein degradation pathways. The metabolic pathways of small molecules (e.g., CYP450 enzymes, glucuronosyl transferases) do not contribute to its elimination.

Elimination

Clearance values range from 2.04 to 2.52 mL/day/kg, and the half-life is 23.4 days (23% CV) in patients with plaque psoriasis.

4.4.3 Efficiency data ^{39–43}

- ReSURFACE 1 is a Phase III, superiority, randomized, double-blind, multicenter, parallel-group study lasting 64 weeks, comparing Tildrakizumab at doses of 100 mg and 200 mg to placebo. The primary objective was to demonstrate the superiority of Tildrakizumab over placebo in adult patients with moderate to severe plaque psoriasis requiring systemic therapy or phototherapy.
- ReSURFACE 2 is a Phase III, superiority, randomized, double-blind, multicenter, parallel-group study lasting 52 weeks, comparing Tildrakizumab at doses of 100 mg and 200 mg to placebo and to Etanercept 50 mg, with an extension phase of 192 weeks. The objective of ReSURFACE 2 was to demonstrate the superiority of Tildrakizumab compared to placebo in adult patients with moderate to severe plaque psoriasis requiring systemic therapy or phototherapy. The comparison with Etanercept was a secondary objective of the study.

These two studies included a total of 1,862 patients aged 18 years and older, with plaque psoriasis covering at least 10% of the body surface area, a PGA (Physician Global Assessment) score ≥ 3 on a scale of 0 to 5 (plaque thickness, erythema, and scaling), a PASI (Psoriasis Area and Severity Index) score ≥ 12 , and requiring phototherapy or systemic treatment.

The overall and baseline demographic characteristics in the ReSURFACE 1 **and** ReSURFACE 2 studies were homogeneous within each study. Patients were aged 18 to 82 years, with a mean age of 45.9 years. The median PASI score at baseline ranged from 17.7 to 18.4 across the treatment groups. The PGA score at baseline was

moderate or severe (≥ 4) in 33.4% of patients. Among all patients, 33.5% had previously received conventional systemic treatment (excluding phototherapy), and 16.7% had received a biological treatment. A total of 15.4% of the patients studied had a history of psoriatic arthritis.

The ReSURFACE 1 and ReSURFACE 2 studies assessed changes from baseline to week 12 with two primary endpoints: PASI 75 and PGA 0 (clear) or PGA 1 (minimal lesion), with an improvement of at least 2 points from baseline. Other outcomes included the percentage of patients achieving PASI 90, PASI 100, the percentage of patients with a DLQI score of 0 or 1, and the maintenance of efficacy up to 52/64 weeks.

The results for each study at weeks 12 and 28 are presented in Table 1, and the maintenance of response is shown in Table 2.

Table 1 Response Rates in the ReSURFACE 1 and ReSURFACE 2 Studies (Weeks 12-28)

	Week 12 (2 doses)				Week 28 (3 doses)		
	100mg	200mg	Placebo	Etanercept	100mg	200mg	Etanercept
reSURFACE1							
Number of patients	308	309	154	-	298	299	-
PASI 75a (%)	62,3 ^{†b}	63,8 ^{†b}	5,8 ^b	-	81,9 ^c	80,4 ^c	-
PGA « clear » or « minimal lesion » with an improvement ≥ 2 from baseline ^a (%)	59,1 ^{†b}	57,9 ^{†b}	7,1 ^b	-	69,1 ^c	66,0 ^c	-
PASI 90 (%)	35,4 ^{†b}	34,6 ^{†b}	2,6 ^b	-	59,0 ^c	51,6 ^c	-
PASI 100 (%)	14,0 ^{†b}	13,9 ^{†b}	1,3 ^b	-	31,5 ^c	23,5 ^c	-
DLQI 0 or 1 (%)	44,2 [†]	41,5 [†]	5,3	-	56,7 ^c	52,4 ^c	-
reSURFACE2							
Number of patients	314	307	156	313	299	294	289
PASI 75a (%)	65,6 ^{††b}	61,2 ^{††b}	5,8 ^b	48,2 ^b	72,6 ^{†b}	73,5 ^{†b}	53,6 ^b
PGA « clear » or « minimal lesion » with an improvement ≥ 2 from baseline ^a (%)	59,2 ^{††b}	54,7 ^{†b}	4,5 ^b	47,6 ^b	69,2 ^{†b}	64,6 ^{†b}	45,3 ^b
PASI 90 (%)	36,6 ^{††b}	38,8 ^{††b}	1,3 ^b	21,4 ^b	57,7 ^{†c}	55,5 ^{†c}	29,4 ^c
PASI 100 (%)	11,8 ^{††b}	12,4 ^{††b}	0	4,8 ^b	27,0 ^{†c}	22,8 ^{†c}	10,7 ^c
Score DLQI 0 or 1 (%)	47,4 ^{††}	40,2 [†]	8,0	35,5	65,0 ^{†c}	54,1 ^{†c}	39,4 ^c

^a Primary efficacy endpoint at week 12.

^b Imputation as non-responder due to missing data.

^c No imputation for missing data.

* The number of doses administered refers only to the groups treated with Tildrakizumab.

n = number of patients in the total population for the analysis for whom data were available, after imputation if applicable.

† p ≤ 0.001 versus placebo ; ‡ p ≤ 0.001 versus Etanercept; ¥ p ≤ 0.05 versus Etanercept.

Table 2 Maintenance of Response in the ReSURFACE 1 and ReSURFACE 2 Studies (Weeks 52-64)

	Long term response ^{a, b}			
	200mg		100mg	
reSURFACE 1	Week 28	Week 64	Week 28	Week 64
Number of patients	116	114	115	112
PGA « clear » or « minimal lesion » with improvement ≥ 2 from Baseline (%)	80,2	76,3	80,9	61,6
PASI 90 (%)	70,7	74,6	65,2	58,0
PASI 100 (%)	38,8	40,4	25,2	32,1
reSURFACE 2	Week 28	Week 52	Week 28	Week 52
Number of patients	108	105	213	204
PGA « clear » or « minimal lesion » with improvement ≥ 2 from Baseline (%)	88,0	84,8	84,0	79,4
PASI 90 (%)	75,0	81,9	74,2	78,4
PASI 100 (%)	34,3	46,7	30,2	35,3

a. Long-term response in patients who were responders (achieved at least a PASI 75 score) under Tildrakizumab at week 28.

b. No imputation for missing data.

During the extension period, efficacy analyses from the pooled data of both trials included 329 and 227 responders at week 28 who had received Tildrakizumab at doses of 100 mg and 200 mg, respectively, as well as 121 partial responders/non-responders to Etanercept treatment who switched to Tildrakizumab 200 mg at week 28. Among the responders to 100 mg, 200 mg, and partial responders to the comparator who switched to Tildrakizumab during the extension phase, 88.7%, 92.5%, and 81.3%, respectively, maintained a PASI 75 response at week 244⁴⁴.

- In a retrospective study ⁴² conducted in the United Kingdom across four sites, 122 patients with moderate to severe plaque psoriasis were included. Of these, half had previously received a biologic therapy. 72% had comorbidities, and 62% had a body weight greater than 90 kg. Among the 75% of patients treated with Tildrakizumab for the 27 months of the study, the PASI score improved from 12 at baseline to 0.35 at the end of the study. The median DLQI score improved from 20 to 0. Furthermore, this

study demonstrated good tolerance to Tildrakizumab, with 5% of patients experiencing adverse events, regardless of the dose administered.

- A study pooling the results of the three clinical trials ReSURFACE 1, ReSURFACE 2, and a Phase 2b trial⁴³ showed that in patients with moderate to severe plaque psoriasis and a body weight >90 kg, Tildrakizumab at a dose of 200 mg was more effective.

4.4.4 Safety profile

The most frequently observed adverse events with Tildrakizumab in the ReSURFACE 1 and ReSURFACE 2 studies were infections ($\geq 1/10$), primarily upper respiratory tract infections such as rhinosinusitis, and less frequently ($\geq 1/100$ and $< 1/10$), injection site reactions, gastrointestinal disorders (diarrhea, nausea, and gastroenteritis), headaches, and back pain. Among the most common adverse events of interest, the occurrence of serious infections, cardiovascular events, including major cardiovascular events, malignancies, and a few cases of non-melanoma skin cancers and melanomas were noted. However, the analysis of these data did not support them as established risks, but they are considered as potential risks. The 4-year extension studies confirmed the safety profile observed in the initial phases of these studies. The development of anti-Tildrakizumab antibodies over 52 to 64 weeks was low, around 3%, with no observed correlation between antibodies and safety.³⁹

The 5-year safety profile of Tildrakizumab was studied in the ReSURFACE 1 and ReSURFACE 2 trials, in comparison to reference data from the PSOLAR registry, which tracks long-term safety data for both biologic and non-biologic treatments administered for psoriasis. This study demonstrated a favorable safety profile over 5 years, with low rates of adverse events of particular interest, comparable to those observed in the PSOLAR registry⁴⁵.

4.4.5 Impact on quality of life

In the ReSURFACE 1 and ReSURFACE 2 studies, Tildrakizumab was associated with a statistically significant improvement in health-related quality of life, as assessed by the DLQI at weeks 12 and 28 (Table 1). Quality of life improvements were maintained over time, with at week 52, 63.7% (100 mg) and 73.3% (200 mg) (ReSURFACE 1), and 68.8% (100 mg) and 72.4% (200 mg) (ReSURFACE 2) of PASI 75 responders at week 28 maintaining a DLQI score of 0 or 1⁴⁶. The UK study also showed a notable

improvement in DLQI, with the median score dropping from 20 at baseline to 0 at the end of the 29-month study.

4.4.6 Real life data

Overall, the previously cited UK retrospective study and the ReSURFACE 1 and ReSURFACE 2 trials, two international multicenter studies, demonstrated the efficacy and safety of Tildrakizumab, as well as an improvement in quality-of-life outcomes. In patients with certain characteristics (e.g., high comorbidity burden, body weight ≥ 90 kg), Tildrakizumab 200 mg may provide greater efficacy^{42,43,47}. However, real-world data on the effectiveness of Tildrakizumab 200 mg in unselected patients is still limited. Cependant les données en vie réelle sur l'efficacité du Tildrakizumab 200mg avec des patients non sélectionnés sont encore limitées.

5. STUDY OBJECTIVES

The objective is to evaluate the efficacy, safety, and flexibility of Tildrakizumab in a cohort of patients with moderate to severe plaque psoriasis, with a high comorbidity burden and/or a body weight ≥ 90 kg.

5.1 Main objective

The primary objective is to assess the efficacy of Tildrakizumab 200mg at week (W)28.

5.2 Secondary objectives

Secondary objectives are :

- 1/ Evaluate the maintain of efficacy of Tildrakizumab at W52 and W76.**
- 2/ Evaluate the maintenance of efficacy of Tildrakizumab in case of dose reduction of Tildrakizumab by dermatologist** (from Tildrakizumab 200 mg to Tildrakizumab 100mg).
- 3/ To study the quality of life and general well-being** and their evolution while treatment.
- 4/ To study the safety of Tildrakizumab** and occurrence of adverse events throughout follow-up.

5.3 Exploratory objectives

Exploratory objectives are:

- 1/ To study and describe contributing elements to disease burden in real-life.

2/ Identify participants profiles according to rapidity of response to treatment, its maintenance throughout follow-up and contributing elements to disease burden identified.

3/ Identify the delay and associated conditions to dose change of Tildrakizumab.

5.4 Main criteria

The response to Tildrakizumab will be assessed by « PASI absolute (Psoriasis Area and Severity Index) » at W28

5.5 Secondary and exploratory endpoints

5.5.1. Secondary efficacy endpoints

Maintenance of treatment response will be assessed by PASI absolute at W52 and W76 according to Tildrakizumab dose (200mg or 100mg).

For patients with difficult-to-treat areas (nails, scalp, palmoplantar, genital region), the response will be adjusted based on the specific response determined by the investigator physician, considering either complete or near-complete lesion clearance, expressed as the average percentage decrease in the PGA score or an equivalent score depending on the location:

- Target site at the nail: Finger nail PGA equal to 0 or 1, or a decrease of at least 2 points from baseline visit.
- Target site on the scalp: Scalp PGA equal to 0 or 1, or a decrease of at least 2 points from baseline visit.
- Target site in the genital area: sPGA-G score equal to 0 or 1, or a decrease of at least 2 points from baseline visit.
- Target site in the palmoplantar area: PP-PGA score equal to 0 or 1, or a decrease of at least 2 points from baseline visit.

5.5.2 Safety criteria

To address the safety objectives, the nature and frequency of adverse events at the different visits will be described.

5.5.3 Psychosocial impact and well-being

The criteria used to assess the impact of treatment on perceived quality of life and well-being will include:

- Changes in the DLQI (Dermatology Life Quality Index) score between baseline and subsequent visits.

- Description of each dimension of the DLQI.
- Changes in the well-being score assessed by the WHO-5 Well-Being Index between baseline and subsequent visits.

Treatment adherence and premature discontinuation will also be taken into account for all of these criteria.

Physical inactivity will be assessed using a self-administered physical activity questionnaire at visits W0 and W72.

5.5.2 Exploratory criteria

Psoriasis is associated with a high rate of various complications and is considered an independent risk factor for death, which complicates its management. Some studies showing an association between the severity of psoriasis and the risk of cardiovascular comorbidities have used the Psoriasis Area and Severity Index (PASI) score as a measure of psoriasis severity. Other studies have shown an association between body surface involvement and cardiovascular risk. Currently, it is unknown whether PASI or body surface area is more closely correlated with cardiovascular risk in patients with psoriasis ¹⁰.

The disease burden will be explored based on the patient's notable conditions (medical history and comorbidities), previous treatment failures for psoriasis, disease severity, polypharmacy, functional symptoms, body surface area, and perceived quality of life and well-being.

6. STUDY DESIGN

TILFLEX is a French, prospective, multicenter Phase IV observational postmarketing follow-up study in patients with moderate to severe plaque psoriasis associated with a high disease burden.

The total duration of follow-up for participants in the study will be 76 weeks, with the primary endpoint assessed at week 28. The inclusion period will be 10 months.

7. STUDY POPULATION

Seront éligibles les patients répondant à tous les critères d'inclusion et à aucun des critères de non-inclusion suivants :

7.1. Inclusion criteria

1. Patient with a diagnosis of moderate to severe chronic plaque psoriasis documented in the medical record, defined by:
 - i. PASI $\geq$ 10
 - ii. And/or body surface area (BS) affected $\geq$ 10%
 - iii. And/or DLQI $\geq$ 10
2. Disease diagnosis > 6 months (regardless of severity at diagnosis)
3. Body weight $\geq$ 90kg and/or a high burden of disease (assessed by physician)
4. Indication for treatment with an IL-23 inhibitor. Tildrakizumab 200mg must be the selected anti-IL-23 therapy prior to enrolling the patient in the study.
5. Patient 18 years of age or older at the inclusion visit
6. French social security affiliation/entitlement

Patients with joint involvement may be included in the study.

7.2. Exclusion criteria

1. Patient unable to comply with study requirements (complete study questionnaires)
2. Patient who, in the opinion of the investigator, should not participate in the study. This opinion should be documented in the patient's record.
3. Patient included in an interventional clinical trial at inclusion. Except in exceptional cases, concurrent participation in an interventional clinical trial will not be possible during the course of the study and must be discussed in advance with the Sponsor. Participation in low and minimally risk studies (such as those evaluating care, for example) or observational studies (such as registries, etc.) is permitted.
4. Vulnerable patient or patient under court protection
5. Patients with known hypersensitivity to IL-23 inhibitors
6. Patients with active HIV, HBV or HCV infection at the time of inclusion
7. Patient with a history of untreated latent tuberculosis or active tuberculosis at inclusion

8. Patient with any other serious active infection* present at inclusion that contraindicates anti-IL23 use.
9. Pregnant or lactating patients at baseline. Patients of childbearing potential will be informed of the need to use effective contraception during treatment**.

La participation à des études à risque et contraintes minimales (évaluant les soins par exemple) ou des études observationnelles (registre, etc.) est autorisée.

** In accordance with the Tildrakizumab Product Monographs, the investigator should ensure the absence of serious progressive infection throughout the follow-up.*

***In accordance with the Tildrakizumab Product Monograph, the investigator must ensure the absence of pregnancy throughout follow-up and the use of an effective method of contraception during treatment with Ilumetri and for at least 17 weeks after treatment.*

8. TREATMENT

8.1 Administration

Treatment with Tildrakizumab (brand name ILUMETRI), presented as an injectable solution, will be administered in accordance with the Summary of Product Characteristics (SmPC).

The initial dose will be 200 mg administered by subcutaneous injection.

A dose adjustment is possible during the study (dose reduction and switch to 100 mg). Dose reevaluation during treatment is at the discretion of the investigator and must be documented in the study's observation notebook.

Treatment should be initiated by week 0, at the latest within 4 weeks after the visit, followed by another dose 4 weeks later, and then every 12 weeks thereafter, according to the SmPC guidelines.

8.2 Stopping criteria

TILFLEX being an observational study conducted in real-life, decisions regarding treatment discontinuation and the associated criteria will be at the discretion of the investigator.

Permanent discontinuation of treatment will be considered a reason for study withdrawal. However, the reason and the date of discontinuation must be thoroughly recorded.

In the case of a temporary treatment interruption, the patient will remain in the study.

The reasons for temporary discontinuation, the dates, and the resumption doses will be collected, and follow-up visits will be conducted until the S76 visit (theoretical date).

8.3 Other treatments

Since **TILFLEX** is an observational study, participants are allowed to receive supportive treatments for psoriasis or other treatments for other conditions. The prescription, continuation, or discontinuation of concomitant treatments is at the discretion of the investigator. These treatments will be recorded in the Case Report Form (CRF).

9. STUDY PROCEDURE

9.1 Selection/ patient inclusion

Around thirty centers in France will participate in the study. The inclusion phase, which will last 10 months, will be competitive between centers, with inclusion stopping once 120 participants have been reached. The investigative centers will be the departments of hospitals, clinics, or specialized dermatology care centers that treat patients with moderate to severe plaque psoriasis.

Patients who meet the eligibility criteria and have not objected will be able to participate in the study. To minimize selection bias, the study will be offered consecutively throughout the recruitment period to all eligible patients, with careful documentation of patients who were selected but not included, along with reasons for non-inclusion (see Section 11.2.4).

Before any intervention, test, or procedure specific to the study, participants will be informed about the objectives and specific procedures of the study. An information notice will be provided, and the investigator will ensure that there is no objection to participation. The investigator will ensure that all questions from participants regarding the study are answered and that they are given sufficient time to reflect on their decision. This reflection period will be decided on a case-by-case basis by the investigator, depending on the patient's understanding. This information will be documented in the patient's medical record.

9.2 Conduction of visits

The patients' participation in the study will last 76 weeks, with four on-site visits: at baseline (W0), W28, W52, and W76.

9.2.1 Baseline (W0)

During this visit, the investigator will ensure the following steps are completed:

- Validation of eligibility criteria
- Provision of information and collection of non-opposition
- Traceability of information given and collection of non-opposition in the patient's file
- Collection of the following information (if not available in the medical file):
 - Age, sex
 - Family history
 - Personal medical history
 - Lifestyle
 - Date of psoriasis diagnosis
 - Previous treatments for psoriasis
 - Ongoing treatments
 - Comorbidities assessment
- Conduct of a clinical examination (including recording weight and height)
- Psoriasis evaluation: documenting the locations of psoriasis and signs of psoriatic arthritis, functional symptoms, and lesion characterization using the following scores:
 - **Psoriasis Area and Severity Index (PASI)**
 - **Physician Global Assessment (PGA)**

For patients with potentially difficult-to-treat locations, evaluation using the following specific scores:

- **Nail** : Finger Nail PGA (f-PGA)
- **Scalp** : Scalp PGA
- **Palmo-plantar**: Palmoplantar PGA (PP-PGA)
- **Genital**: Static Physician's Global Assessment of Genitalia (sPGA-G)
- Provision of self-administered questionnaires: DLQI, WHO-5, and physical activity assessment

-
- Biological assessment (according to standard protocols)
 - Prescription of Tildrakizumab.

Note: According to standard care, the investigator must ensure the absence of active severe infections contraindicating the use of Tildrakizumab and confirm the absence of pregnancy in women of childbearing age, with the possible implementation of effective contraception for women of childbearing potential.

Tildrakizumab should be initiated no later than 4 weeks after the baseline visit (W0), then administered every 12 weeks according to the prescribing information. The initial dose is 200 mg, with dose adjustments during treatment at the investigator's discretion, but must be strictly documented.

9.2.2 Visit at Week 28 after the start of treatment (+/- 4 weeks)

- Conduct of a clinical examination (including recording weight)
- Collection of Adverse Events (AEs) since the previous visit
- Collection of ongoing psoriasis treatments
- Comorbidities assessment
- Global psoriasis evaluation: functional symptoms and use of the following scores:
 - **Psoriasis Area and Severity Index (PASI)**
 - **Physician Global Assessment (PGA)**

For patients with difficult-to-treat locations, evaluation using the following specific scores:

- **Nail** : Finger Nail PGA (f-PGA)
- **Scalp** : Scalp PGA
- **Palmo-plantar**: Palmoplantar PGA (PP-PGA)
- **Genital**: Static Physician's Global Assessment of Genitalia (sPGA-G)
- Reevaluation of Tildrakizumab dose
- Provision of self-administered questionnaires (DLQI, WHO-5, adherence)

9.2.3 Visit at Week 52 after the start of treatment (+/- 4 weeks)

- Conduct of a clinical examination (including recording weight)
- Collection of Adverse Events (AEs)
- Collection of ongoing psoriasis treatments

- Comorbidities assessment
- Global psoriasis evaluation: functional symptoms and PASI and PGA scores

For patients with difficult-to-treat locations, evaluation using the following specific scores:

- **Nail** : Finger Nail PGA (f-PGA)
- **Scalp** : Scalp PGA
- **Palmo-plantar**: Palmoplantar PGA (PP-PGA)
- **Genital**: Static Physician's Global Assessment of Genitalia (sPGA-G)
- Reevaluation of Tildrakizumab dose
- Provision of self-administered questionnaires (DLQI, WHO-5, adherence)

9.2.4 Visit at Week 76 after the start of treatment (+/- 4 weeks)

- Conduct of a clinical examination (including recording weight)
- Collection of Adverse Events (AEs)
- Collection of lifestyle information
- Collection of ongoing psoriasis treatments
- Collection of ongoing treatments
- Comorbidities assessment
- Global psoriasis evaluation: functional symptoms and PASI and PGA scores

For patients with difficult-to-treat locations, evaluation using the following specific scores:

- **Nail** : Finger Nail PGA (f-PGA)
- **Scalp** : Scalp PGA
- **Palmo-plantar**: Palmoplantar PGA (PP-PGA)
- **Genital**: Static Physician's Global Assessment of Genitalia (sPGA-G)
- Provision of self-administered questionnaires (DLQI, WHO-5, adherence, physical activity assessment).

Table 3 – Visit Schedule

	Baseline (W0)	S28 (+/- 4 sem)	Visite S52 (+/- 4 sem)	Visite S76 (+/- 4 sem)
Validation of eligibility criteria	X			
Providing information and collection of participant's non-opposition	X			
Collection of demographic data	X			
Collection of personal and family history personnels	X			
Collection of previous psoriasis treatments	X			
Lifestyle (smoking, alcohol, sedentary lifestyle)	X			X
Collection of ongoing psoriasis treatments	X	X	X	X
Collection of ongoing concomitant treatments	X			X
Characterization of psoriasis	X			
Assessment of comorbidities	X	X	X	X
Clinical exam with weight measurement (and height at W0 only)	X	X	X	X
General assessment of psoriasis: PASI, PGA, functional signs, specific ⁱⁱ	X	X	X	X
Tildrakizumab 200 mg prescription	X			
Self-administred questionnaires : DLQI et WHO-5	X	X	X	X
Compliance questionnaire		X	X	X
Physical activity questionnaire	X			X
Collection of adverse events (AE)		X	X	X
Tildrakizumab dose reevaluation and prescription		X	X	X

¹ For patients with difficult-to-treat locations: nail : f-PGA, scalp : scalp PGA, palmoplantar : PP-PGA, genital : sPGA-G

9.3 Data Collection

9.3.1 Clinical data

Patient historical and medical data will be collected from medical records or directly gathered by the investigators during the visits. Psoriasis assessment data will be collected directly from the forms in the paper CRF and will then constitute the source data (see Section 12.1).

9.3.2 Data collected from the patients

Data collected from the patients (Patient Reported Outcomes PROs) will be recorded using self-administered questionnaires (Annexe II)

Tableau 4 – Description des PROs recueillis pour l'étude TILFLEX

Questionnaire	Frequency	Justification
Quality of life – DLQI	At each visit (W0, W28, W52, W76)	Significant psychosocial impact of the disease ^{48,49} . Estimate the potential impact of treatment and the progression of psoriasis on quality of life.
WHO-5	At each visit (W0, W28, W52, W76)	Measure psychological well-being and its progression during treatment
Treatment compliance	At each follow-up visit (W28, W52, W76)	Assess the treatment adherence as reported by the patient for the estimation of efficacy criteria.
Physical activity assessment	At baseline and last follow-up visit	Evaluate the risk factors related to physical inactivity.

9.4 Study discontinuation

In case of study discontinuation, the investigator will promptly inform the Sponsor or their representative. The date of the last contact and the reasons for study discontinuation will be recorded in the CRF.

9.4.1 Permanent discontinuation of Tildrakizumab

The permanent discontinuation of Tildrakizumab constitutes an exit criterion from the study (see Section 8.2 Exit Criteria). This treatment discontinuation will be reported to the sponsor using the dedicated forms (treatment end and study end, safety event/special situation declaration, if applicable). Information regarding the discontinuation and any subsequent therapies will be collected. Safety events will continue to be collected up to 30 days after the last administration of Tildrakizumab (see Section 15.3 Reporting of Adverse Events/Special Situations). From the date of study exit, except for the follow-up of adverse events, clinical data from subsequent follow-up visits will no longer be collected as part of the study.

9.4.2 Consent withdrawal

A patient wishing to withdraw his consent to participate in the research (opposition to the use of his data), as he is entitled to do at any time, will no longer be followed as part of the study but will continue to receive the best possible care based on their health status and the state of scientific knowledge at the time of withdrawal. From the date of opposition, no further data should be collected for the study. If applicable, any follow-up data collected after the patient's stated date of opposition should be permanently deleted from the study database. Data collected up until the date of opposition will be retained and analyzed for research purposes.

In general, withdrawals should be reported to the CRO as quickly as possible. The date of opposition must be documented in the CRF and the source file. Whenever possible, the investigator will also provide the reasons for withdrawal, if known.

9.4.3 Change of care location / Inhability to travel

In the situation where a participant changes their follow-up center for psoriasis, the Sponsor and the CRO must be promptly informed.

If the new care center is participating in the TILFLEX study, the Sponsor or their representative will instruct the investigators on the procedure to follow in order to allow the participant to change follow-up centers during the study.

If the new center is not part of the study, the patient will be considered to have exited the study.

In the situation where the participant declares that they are physically or materially unable to attend their follow-up visits in the study, the patient will be considered to have exited the study.

9.4.4 Lost of follow-up

When a participant misses a follow-up visit, the investigational site must make every effort to contact the participant and determine the reason for their absence. If possible, a new visit will be rescheduled. The CRO must be promptly informed of any missed visits.

A patient will be considered lost to follow-up if, despite three documented contact attempts, the investigator does not receive any news from the patient for more than 12 months. Participants lost to follow-up during the study will be reported in the participant's CRF.

9.4.5 Investigator's choice / other Reasons

At the investigator's discretion and/or if the participant's health condition requires it, the patient may exit the study. The reason will be documented in the participant's CRF and source file.

In the case of a major deviation, particularly regarding eligibility criteria, the Sponsor or the CRO may suspend the patient's participation in the study (see Section 10)

10. PROTOCOL DEVIATIONS

Failure to comply with the protocol, standardized operating procedures, good clinical practices, or applicable legislative and regulatory provisions by an investigator, a sponsor staff member, or any other person involved in the conduct of

the research must promptly result in the implementation of appropriate measures by the sponsor.

No deliberate deviation from the protocol will be permitted by the sponsor.

The investigator agrees to adhere to the provisions of the protocol, particularly regarding the conditions for conducting the research and the methods for expressing and publishing the results.

However, in the event of a retrospective discovery of a protocol deviation, the investigator, or any person designated by them, must justify, document, and promptly transmit the information to the sponsor.

Deviations and non-compliance with applicable standards are classified into three categories:

Minor: Conditions, practices, or processes that are unlikely to harm the rights, safety, or well-being of the subjects, or affect the quality and integrity of the data.

Major: Conditions, practices, or processes that could harm the rights, safety, or well-being of the subjects, or affect the quality and integrity of the data.

Critical: Conditions, practices, or processes that harm the rights, safety, or well-being of the subjects, or affect the quality and integrity of the data. Critical findings are considered completely unacceptable.

Depending on the deviation, the affected participant's participation may be stopped.

If a serious or deliberately repeated deviation by an investigator or any other person involved in the research is detected during research monitoring, quality control, or an audit, the sponsor may end the site's participation.

11. STATISTICAL CONSIDERATIONS

11.1 General considerations

TILFLEX is an observational study, the main results will be presented by descriptive tables.

The characteristics of the patients will be summarized overall. The baseline variables will include, in particular, patient characteristics, notable medical history, psoriasis characteristics and comorbidities assessment. Previous treatments for psoriasis will also be summarized overall and described according to the treatment response. Since the study is descriptive, continuous variables will be summarized using descriptive statistics (number of observations, mean, standard deviation, median, interquartile range (Q1, Q3), range) according to the nature of the data distribution, which will be verified by a Lilliefors test. Student's t-test or ANOVA will be used to compare groups, provided that the distributions are Gaussian; otherwise, Kruskal-Wallis tests will be performed. Frequency (number and percentage) will be summarized for categorical and discrete variables. Pearson's Chi-square test or Fisher's exact test will be used to compare distributions based on the groups being compared.

If patients lost to follow-up at S76 represent more than 10% of the study population, their sociodemographic characteristics and baseline characteristics will be described and compared to those of patients not lost to follow-up using the same methodology outlined above. All statistical significance tests will be two-sided at the 95% confidence level. The error rate for statistical tests will be set at 5% for two-sided tests.

11.2 Statistical analysis

11.2.1 Primary analysis

"The primary analysis will estimate the percentage of response in absolute PASI categorized at S28, along with its 95% confidence interval using the Clopper-Pearson method. Univariate linear regressions on the absolute PASI at S28 may be performed to study the effect of disease burden on the response. A multivariate model may be proposed if necessary, with an appropriate strategy (including the potential use of a selection algorithm).

11.2.2 Secondary analysis

For the analysis of secondary endpoints, the psoriasis assessment parameters, quality of life, and well-being will be described and compared at each time point and according to the dose received, using the same methodology as in section 11.1. The percentage of response will be described based on the absolute PASI, categorized

by subgroups according to relevant criteria (difficult-to-treat locations, BMI categories, psoriasis severity, etc.).

The evolution of mean PASI scores between baseline and different visits will be studied using analysis of variance (mixed ANOVA for repeated measures, followed by mean comparisons using the least squares method) to take account the dose of Tildrakizumab used (100 mg or 200 mg) and treatment adherence.

Disease burden will be estimated from comorbidities and patient history, failure of previous psoriasis treatments, body surface area, polymedication and functional signs.

To choose the best model to study maintaining of efficacy, temporal analyses and Sankey plots will be created.

For the other secondary criteria, parameters will be described and compared at each time point. The overall score from the DLQI (Dermatology Life Quality Index) quality of life questionnaire and the WHO-5 well-being questionnaire will be described at visits W0, W28, W52, and W76. Paired tests, adapted (either parametric or non-parametric) according to their distributions, will be performed to compare the different time periods. Patient profiles based on response will be determined from the maintenance of the absolute PASI (Psoriasis Area and Severity Index) at visits W52 and W76, respectively, taking into account dosage changes.

Patient profiles based on response and disease burden will be explored using multinomial logistic regression models and/or machine learning algorithms such as decision trees (random forest or confidence inference trees).

11.2.3 Analysis population

The analyses will be conducted per protocol (with full follow-up until at least W28 for the main analysis). Sensitivity analyses in an ITT (Intention-to-Treat) population, taking account for any lost to follow-up and early discontinuations, will be conducted as supplementary analyses.

11.2.4 Methods to Limit Selection Bias

To reduce selection bias in the study, the following procedures will be implemented:

- Consecutive, non-selective recruitment

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- Rigorous anonymous collection of data on eligible subjects who were not included (age, sex, reason for non-inclusion)
 - Comparison of the study population characteristics with data from the literature
 - Contacting potential lost to follow-up patients and consulting the national death registry by the centers, if necessary

11.2.5 Management of missing data

Regarding the handling of missing data, the following procedures will be implemented:

- Preventive measures: Limitation of the items to be collected, training of investigators on the CRF (Case Report Form) and good practices for data collection.

- During the study: The collected data will undergo regular quality control (see section 13). In the case of missing data on important key variables, the site will receive enhanced monitoring (on-site or by phone).

- During the analysis: The main analysis will be conducted on complete cases at W28 for the primary endpoint (per protocol).

For the supplementary analyses:

Response scores with missing data but allowing for the minimum score to be obtained will be reclassified. For psoriasis assessment scores, the last available value will be used for response evaluations using the LOCF (Last Observation Carried Forward) method or a regression imputation method (i.e., taking into account the various explanatory variables).

For all other secondary endpoints, missing data will be treated as such, and the analysis will be based on observed data.

11.2.6 Sample size

The study is mainly descriptive, and the sample size has been estimated based on:

- the prevalence of psoriasis with difficult-to-treat locations,
- the capabilities of the selected centers to include these patients.

A total of 120 patients are expected to be included

12. DATA MANAGEMENT

The sponsor or its authorized representative will implement procedures to ensure that the data generated as part of the study is reliable and robust. All information related to the study must be recorded, processed, handled, and stored by the sponsor or the investigator, as appropriate, in such a way that it can be reported, interpreted, and verified accurately, while ensuring the confidentiality of records and personal data of patients is maintained in accordance with applicable personal data protection laws. Furthermore, appropriate technical and organizational measures must be implemented to protect the information and personal data being processed from unauthorized or unlawful access, disclosure, dissemination, alteration, destruction, or accidental loss, especially when the processing involves transmission over a network.

12.1 Source documents requirements

Source documents (whether paper or electronic) are those in which patient data is recorded and documented for the first time. These include, but are not limited to, hospital records, clinical and office records, laboratory notes, memoranda, patient-reported outcomes, assessment checklists, medication dispensing records, data recorded by automated instruments, copies of transcriptions certified as accurate and complete after verification, microfiche, photographic negatives, microfilms, or magnetic media, X-rays, patient records, and records maintained in pharmacies, laboratories, and medical-technical departments participating in a clinical trial. The data collected during this study must be recorded on the appropriate source documents.

To make the verification of source data easier, investigators and institutions must provide the sponsor and its representatives, direct access to the source documents and applicable reports, or certified complete copies, for study-related monitoring, audits, or inspections. The study site must also allow inspection by the competent health authorities. The patient information note will include a statement confirming that the patient does not object that study staff having direct access to the original medical records. This personnel, bound by professional confidentiality, must ensure the confidentiality of any personal identity or medical information (in accordance with confidentiality rules and data protection regulations).

12.2 Case Report Form (CRF)

Data from each visit will be collected on a paper CRF (Case Report Form). A copy will be kept at the site.

It is the responsibility of the investigator to complete the CRFs adequately and accurately in order to record all relevant observations and other data for the study in a timely manner. All CRFs must be filled out in full, in an orderly and legible manner, to ensure accurate interpretation of the data. Copies of the CRFs will be sent to the CRO within 8 days after each visit.

Data entry from the paper CRFs will be centralized by the CRO into a digital solution (eCRF) hosted on servers located in Europe i) accredited as a Health Data Hosting Provider (HDS), ii) compliant with Good Clinical Practice (GCP), iii) and in accordance with MR003 regulations.

The study databases will be encrypted, stored, and archived on servers located in Europe and fully accredited as 100% Health Data Hosting (HDS) with limited access.

In case that a correction is needed on the data, the corrected information will be added to the paper CRF after a visible strike-through and manual initials at the location of the original information, and will be overwritten in the centralized eCRF. An audit trail will allow identification of the modification and facilitate comparison with the original paper CRFs. The paper CRFs (pCRFs) will be retained for the same duration as the essential study documents.

12.3 Data quality assurance

The CRO will be responsible for managing the data for this study, including data quality control. Data entered manually will be collected via paper CRFs and then entered into an e-CRF. In case of divergent data, the CRO will ask the sites to clarify the data. The sponsor will oversee the management of the study data. The e-CRFs and correction documents will be retained, along with the system audit trail (see section 13).

12.4 Archiving

The investigator is responsible for the storage and archiving of all study records at their site during and after the study, in accordance with ICH-GCP guidelines.

According to current regulations, essential documents must be retained for at least 15 years after the completion of the study.

13. QUALITY CONTROL AND ASSURANCE

Data quality will be assessed through:

- Consistency checks of the data,
- Descriptive statistical reviews of the data,
- Monitoring of key source data.

The consistency check, both on paper CRFs before data entry and electronically after entry, involves sending queries to investigators in case of missing data or identified inconsistencies.

Periodic statistical reviews of the data will help reinforce consistency checks and provide key performance indicators for the participating sites regarding data quality.

A site quality control, based on comparisons with source data, will be conducted on key study data. The percentage of monitoring of key data from the source file will be tailored to the study's risk profile and adjusted according to performance indicators of the sites, which will be measured throughout the study and defined according to a monitoring plan established prior to the study's initiation.

The investigator must ensure compliance with all the procedures required by the study, as well as all study procedures provided by the Sponsor (including safety protocols). The investigator agrees to provide reliable data and all information requested by the study protocol in an accurate and legible manner, according to the provided instructions, and to ensure direct access to source documents for the Sponsor's representatives.

The investigator must facilitate the monitoring of their site by attempting to establish schedules for monitoring visits with the Clinical Research Associate (CRA) assigned to their site. During these monitoring visits, the investigator and their team must be available and provide all documentation and information required by the CRA.

The Sponsor is responsible to the regulatory authorities for taking all reasonable measures to ensure the proper conduct of the clinical study in terms of ethics, adherence to the study protocol, and the integrity and validity of the data recorded on the CRF. Therefore, the main task of the monitoring team is to assist the investigator

and the sponsor in maintaining a high level of ethical, scientific, technical knowledge, and regulatory quality in all aspects of the study.

At regular intervals during the clinical study, the site will be contacted via monitoring visits, emails, or phone calls by a representative of the monitoring team to review the progress of the study, adherence to the study protocol requirements concerning patients and the investigator, as well as any emerging issues. These monitoring visits will include, but are not limited to, the review of the following aspects: patient information, informed consent, patient recruitment and follow-up, documentation and reporting of AEs/SAEs, and data quality.

14. FEASIBILITY – STUDY TIMELINE

The study is scheduled to start in Q4 2024. The inclusion period will last 10 months. The active phase (clinical follow-up) of this study is expected to last approximately 30 months.

The duration of participation for each patient will be 76 weeks (approximately 18 months).

15. MANAGEMENT AND DECLARATION OF ADVERSE EVENTS AND SPECIAL SITUATIONS

The investigators will closely monitor adverse events/special situations and take clinical measures to ensure patient safety.

15.1 Definitions

Adverse events (AE)

An adverse event (AE) is any unfavorable medical that occur in a study participant who has been administered a drug, and which may not necessarily have a causal relationship with the treatment. An AE can thus be any unfavorable or unexpected sign (including an abnormal laboratory result), symptom, or illness temporarily associated with the use of a drug, whether or not it is considered to be related to the drug.

Adverse drug reaction (ADR)

An adverse drug reaction, unlike an adverse event, is characterized by a suspected causal relationship between the drug and the event. For regulatory reporting purposes,

if an event is reported spontaneously, even if the relationship is unknown or not stated by the healthcare professional or consumer as the primary source, it will be classified as an adverse drug reaction. Therefore, all spontaneous reports from healthcare professionals or consumers will be considered suspected adverse drug reactions, as they reflect the assumptions of the primary sources, unless they explicitly indicate that they believe the event is unrelated or that a causal relationship can be excluded.

Adverse drug reactions can result from the use of the product within or outside the terms of the marketing authorization or from professional exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse, and medication errors.

Serious adverse event (SAE) / Serious adverse drug reaction (SADR)

A serious adverse event (SAE) or a serious adverse drug reaction (SADR) is an adverse event or adverse drug reaction that falls into one or more of the following categories:

- Results in death
- Is life-threatening. In this context, "life-threatening" refers to a reaction where the patient was in imminent danger of death at the time of the reaction; it does not refer to a reaction that could have hypothetically caused death if it had been more severe.
- Requires hospitalization or prolongs an existing hospitalization: Hospitalization is defined as an overnight stay in a hospital or emergency department. Prolonged hospitalization is defined as any extension of a hospital stay beyond what was initially planned or necessary, based on the original reason for admission, as determined by the investigator or the treating physician.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect, or
- Represents any other clinically significant event. In such cases, medical and scientific judgment should be applied to determine whether other situations should be considered serious reactions. These may include important medical events that do not immediately result in life-threatening conditions, death, or hospitalization, but could potentially compromise the patient's life or require intervention to prevent one of the other serious outcomes listed above.

Any suspicion of the transmission of an infectious agent through a drug may also be considered a serious adverse event (SAE) or a serious adverse drug reaction (SADR).

Special situations

Any report of lack of therapeutic efficacy, maternal/paternal exposure during pregnancy and breastfeeding, suspected drug interaction, suspected transmission of infectious agents, unexpected therapeutic or clinical benefit resulting from the use of the product, and conditions of exposure such as overdose, off-label use, misuse, abuse, medication error, and occupational exposure, whether or not an adverse event/adverse drug reaction is associated, should also be documented and reported.

15.2 Collection of adverse events (AEs) / Special situations

All Serious Adverse Events (SAEs) (whether serious or not), all Serious Adverse Reactions (SARs) that result in a fatal outcome (regardless of their relationship with the drug under study), and reports of special situations (including pregnancies) must be collected. Adverse events and special situations reported by the patient or observed by the investigator must be documented on the AE page of the CRF (Case Report Form) and should be described as follows:

- The nature of the event will be described using precise and standard medical terminology (i.e., not necessarily with the exact words used by the patient). If known, a specific diagnosis should be recorded instead of listing signs and symptoms (e.g., allergic contact dermatitis).
- The duration of the event will be described by the start date and the end date
- The intensity of the event will be described in terms of severity based on the clinical judgment of the investigator and the following categories:
 - **Mild:** Awareness of an event, symptoms, or signs, but easily tolerated (acceptable).
 - **Moderate:** Sufficient discomfort to interfere with usual activities (disruptive).
 - **Severe:** Inability to work or carry out usual activities (unacceptable)
- The cause-and-effect relationship between the event and the drug will be described in terms of *related/not related*:

-
- **Related:** Adverse events for which there is strong evidence and sufficient information (e.g., plausible temporal sequence, dose-response relationship, pharmacology, positive administration and/or re-administration) to suggest a cause-and-effect relationship with the drug in terms of plausibility, conceivability, or likelihood.
 - **Not Related:** Adverse events for which solid arguments and sufficient information (e.g., implausible temporal sequence and/or attributable to a concomitant disease or other medications) allow for the exclusion of a cause-and-effect relationship with the drug.

If the events are evaluated as not related to the drug, the event is not considered reportable. In the absence of causality information from the reporting investigator, the CRO will immediately contact the reporting investigator to request an evaluation of causality. The report will be updated with the follow-up information and reported accordingly. If no causality link is provided by the investigator, the sponsor's evaluation will be considered for submission purposes.

The outcome of the event will be described in terms of:

- **Resolved:** The event has completely resolved.
- **Improving:** The event has improved compared to the previous observation (e.g., decrease in intensity, improvement in laboratory test results).
- **Resolved with sequelae:** The event has resolved but permanent sequelae remain.
- **Unresolved:** The event has not changed or has worsened compared to the previous observation.
- **Death:** The patient has died.
- **Unknown:** Unknown at the time of reporting.

The action taken regarding the drug will be indicated as follows:

- **Discontinuation of the drug**
- **Dose reduction**
- **Dose increase**
- **No change in dose**
- **Not applicable**

15.3 Adverse events declaration / Special situations

Adverse events/special situations will be collected from the first administration of the drug until 30 days after the last administration of the drug. Any adverse event/special situation reported by the patient from the last contact with the study (follow-up phone call or visit) up to the 30th day must be recorded in the CRF.

Illnesses present at the time of the collection of the informed consent that are part of the patient's medical history will only be considered as adverse events if they worsen after this period.

Abnormalities detected before the first administration of the drug will not be considered as adverse events (AEs) if they are already known as part of the medical history or related to previous medical conditions and will be recorded in the 'Medical History/Physical Examination' section of the CRF.

Abnormalities (new or worsening of previously known abnormalities) detected after the first administration of the drug, which are considered clinically relevant by the investigator or require intervention or diagnostic testing, or which may lead to discontinuation of the drug, must be reported as AEs.

The reported terms must precisely characterize the adverse event. When a patient presents with an injury, signs, or unspecified symptoms, an active investigation must be conducted to reach a final diagnosis. The diagnosis of the disease is the term to be preferred for reporting.

Adverse events (AEs) are collected by asking patients open questions (e.g., 'How are you feeling?') and by gathering AEs spontaneously reported by the patient to the investigator or a person designated by the investigator.

All AEs reported by the investigator during the defined AEs collection period must be recorded in the CRF. Additionally, the following items must also be reported on the 'NIS safety reporting form' and notified within the timeframes defined in section 15.4 :

- Any AE meeting the criteria of relatedness (i.e., an AE that is related), regardless of its severity,
- Any AE with a fatal outcome (whether related or not to the drug), and
- Any special situation.

15.4. REPORT TO THE SPONSOR

The following safety data must be reported by the investigator. For each event to be reported, the investigator must provide the required information both in the dedicated section of the CRF and in the 'NIS safety reporting form.' If additional follow-up information is available, the same reporting deadlines apply.

Table 5- Conditions for Reporting a Safety Event

Event reported	Compleet the AE collection page of the CRF	Complete and submit the NIS safety reporting form to the CRO within 24 hours of becoming aware of the event
Adverse Event (AE) (except those with a fatal outcome)	All	No
Adverse Event with a Fatal Outcome	All	All
Adverse Drug Reaction (ADR)	All	All
Special Situation (as defined in section 15.1)	All (associated or not to an AE/ADR)	All (associated or not to an AE/ADR)

The investigator site must submit the 'NIS safety reporting form' to the CRO by email to the following address: tilflex@clin4all.com.

An event reported to the sponsor's/CRO's pharmacovigilance unit that does not meet the safety reporting criteria must be invalidated by the investigator by submitting a follow-up report.

A regulatory report will be prepared by the sponsor. The sponsor will submit a prompt report to the competent authorities in accordance with global and local regulatory requirements, as applicable.

15.5. Follow-up procedure

All ADRs (Adverse Drug Reactions), fatal AEs, and special situations reported, including those that persist after the end of the study, must be followed up until they are resolved, sufficiently characterized, or no further information can be obtained. Furthermore, the Sponsor/CRO may request the investigator to urgently obtain specific follow-up information.

The investigator will monitor any pregnancy until delivery or until the pregnancy is terminated.

16. TASKS AND RESPONSABILITIES

16.1 Sponsor responsibilities

16.1.1 Role of the Sponsor

The sponsor has overall responsibility for the conduct of the study, including ensuring that the study meets international standards and the regulatory requirements of the relevant authorities.

16.1.2 General obligations

Before allowing sites to begin recruiting study participants, the sponsor is responsible for selecting investigators and signing the investigator site agreement with the investigators and/or hospitals.

Additionally, the sponsor must ensure adequate monitoring of the clinical site.

16.1.3 Selection of investigators and clinical sites

The sponsor will select qualified investigators and institutions that have a sufficient patient population to meet the requirements of the study.

16.1.4. Training of the investigator and site staff

The training of the investigator and appropriate site staff is the responsibility of the sponsor and may be provided during an investigator meeting, a site initiation visit, and/or other appropriate training sessions.

The training of site staff who are not present during the site initiation visit will be the responsibility of the investigator.

16.1.5 Documentation

The sponsor will collect, store, maintain, and ensure that the parties concerned complete, maintain, and retain the essential research documents.

16.1.6 Ongoing Benefit-Risk Assessment

The sponsor is responsible for the continuous evaluation of the benefit-risk analysis throughout the study.

16.1.7 Delegation of Sponsor Tasks

For this study, the sponsor has delegated specific tasks to a Clinical Research Organization (CRO). Throughout the protocol, whenever the term 'sponsor' is mentioned, it includes the sponsor's delegate(s) as being responsible.

16.2 Responsibilities of the investigators

The investigators will conduct the study in accordance with this protocol and applicable local regulations.

It is the responsibility of the investigator to:

- Ensure that the patient is properly informed and that there is no objection to participation;
- Complete the case report form (CRF) and record all relevant study data. The investigator will ensure the accuracy and completeness of the information recorded in the CRF;
- Report adverse events (AEs) in accordance with applicable regulations.

17. ETHICAL AND REGULATORY CONSIDERATIONS

This study is a non-interventional research involving human persons (RIHP3) in accordance with Law No. 2012-300 of March 5, 2012, relating to research involving human subjects (known as the Jardé Law), amended by Order No. 2016-800 of June 16, 2016, and the amending implementing decree No. 2047-884 of May 9, 2017, along with subsequent texts including the decrees of April 12, 2018, and thereafter.

17.1 Patient Information Letter and Non-Opposition Form

The investigator is committed to inform the patient clearly and in accordance with the protocol. The investigator will provide the patient with a copy of the information letter. This letter will specify the patient's right to oppose the collection of their data and the conduct of the research. The information letter and the non-opposition form will be reviewed and approved by the sponsor before being submitted to the Ethics Committee (CPP) for approval. The information letter will detail the handling of personal data in accordance with the General Data Protection Regulation (Regulation No. 2016/679 of the European Parliament and Council, known as GDPR)

17.2 Ethics Committee and Competent Authorities

This study can only be implemented after obtaining a favorable opinion from an Ethics Committee (CPP). For this study, approval from the ANSM (French National Agency for Medicines and Health Products Safety) is not required. However, the ANSM will be informed of the conduction of this study by sending the favorable opinion from the CPP and the study synopsis (Article L. 1121-4 of the Public Health Code, paragraph 3)

17.3 Financial agreement

A financial agreement will be established with each participating investigator site to outline the costs associated with conducting this study. The signing of a contract will be a prerequisite to conducting the study.

17.4 Data protection

The implementation of this research involves the processing of personal data. The Sponsor commits to ensuring that this processing complies with the reference methodology MR-003 and adheres to the obligations defined by the General Data Protection Regulation (GDPR) and the French Data Protection Act No. 78-17 of January 6, 1978, as amended by Decree No. 2019-536 of May 29, 2019.

17.5 Privacy and confidentiality

All information collected on individuals participating in the research will remain strictly confidential and coded.

The investigator must make available the documents and individual data strictly necessary for monitoring, quality control (including monitoring), and auditing of the study to authorized persons (persons mandated by the sponsor for quality control and auditing; ANSM inspectors; judicial authority representatives). Any person with access to this data, including the investigator, is bound by professional secrecy. During the study and after its completion, the individual data collected on participants must not, under any circumstances, include personal details such as names, addresses, or any other information allowing direct identification. To ensure this, each participant will be assigned a unique identifier in the study: an anonymous 7-character code (study center number, participant's entry number at the center based on the order of entry into the study, and the first letter of the surname followed by the first letter of the first name):

FR-[] [] [] [] [] [] [] []

Center number entry number 1st letter surname-first name

Only the participant's code will be reported in the case report form (CRF) to preserve their anonymity.

17.6 Audits and inspections

As part of this study, an inspection or audit may take place. The sponsor and/or participating sites must allow access to the data for the inspectors or auditors.

17.7 Premature end of the study or premature closure of a site

The sponsor reserves the right to stop the study at any time; this decision will be communicated in writing to the investigator. Similarly, if the investigator decides to withdraw from the study, they must inform the sponsor's representative in writing. In such cases, the sponsor and investigator must ensure the protection of the participant's interests.

17.8 Archiving

The investigator must keep all study documentation confidential and take necessary measures to prevent accidental or premature destruction of these documents. All study documents and complete medical records of the participants must be kept by the investigator for a minimum of 25 years after the study's completion. However, applicable regulatory requirements should be considered if a longer retention period is necessary. The investigator must inform the sponsor before destroying any essential study documents following one of the events below: the completion or interruption of the clinical study.

If the investigator's personal situation is such that they can no longer ensure the archiving, they must inform the sponsor, and the relevant files should be transferred to a mutually agreed-upon designated person.

The sponsor/CRO will archive the project management documents according to the ongoing archiving procedure. The CRO will retain documents related to study management after the last closeout visit. The sponsor will keep a copy of the pseudonymized database.

18. FINAL REPORT AND PUBLICATION OF RESULTS

The CRO will be responsible for preparing a clinical study report and providing a summary of the study to the Sponsor.

Scientific publications and the authors involved in publications and communications will be selected by the Sponsor.

The Sponsor reserves the right to:

- Use the study results for any regulatory purposes, either in their own name or on behalf of their subsidiaries,
- Include the study results in the medical documentation accompanying their drugs,
- Distribute copies of the publications.

None of these rights may be claimed without the prior written consent of the Sponsor.

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Annexes

Annexe I – Scores d'évaluation du psoriasis

Annexe II – Auto-questionnaires

Annexe I : SCORES D'EVALUATION DU PSORIASIS

1. Indicateurs généraux

a. PASI: Psoriasis Area and Severity Index

Formulaire de calcul de score PASI					
Le score PASI a pour objectif de quantifier de manière objective la sévérité globale des lésions du psoriasis chez un patient. Veuillez compléter les parties : 1. Caractéristiques des plaques et 2. Scores d'atteinte pour chaque région corporelle.					
1.Caractéristiques des plaques	Score d'atteinte	Régions corporelles			
		Tête et cou	Membres supérieurs	Tronc	Membres inférieurs
Erythème	0 = aucun 1 = léger 2 = modéré 3 = sévère 4 = très sévère				
Induration					
Desquamation					
Sous-totaux		A1 =	A2 =	A3 =	A4 =
Multiplier chaque sous-total par le facteur associé à chaque région corporelle					
		A1 x 0.1 = B1	A2 x 0.2 = B2	A3 x 0.3 = B3	A4 x 0.4 = B4
		B1 =	B2 =	B3 =	B4 =
2.Score d'atteinte (%) pour chaque région corporelle (score pour chaque région de 0 à 6)	0 = aucun 1 = 1 à 9% 2 = 10 à 29% 3 = 30 à 49% 4 = 50 à 69% 5 = 70 à 89% 6 = 90 à 100%				
Multiplier chaque sous-total B1, B2, B3 ou B4 par le score d'atteinte déterminé pour chaque région corporelle					
		B1 x score = C1	B2 x score = C2	B3 x score = C3	B4 x score = C4
		C1 =	C2 =	C3 =	C4 =
Le score PASI du patient est la somme de C1 + C2 + C3 + C4				PASI = (0 à 72)	

Ö Fredrikson T, Pettersson U. Severe Psoriasis-Oral Therapy with a New Retinoid. Dermatologica. 1978;157:238-44.

b. PGA : Physician's Global Assessment

Les lésions psoriasiques seront évaluées à l'aide d'une échelle PGA en 6 points. L'évaluateur doit choisir la catégorie qui représente le mieux l'état de toutes les lésions.

Score	Catégorie	Description
0	Blanchi	Aucune manifestation d'érythème mais décolorations résiduelles possibles Aucune manifestation de desquamation Aucune manifestation d'induration
1	Minime	Plaques avec érythème faible Squames fines et occasionnelles pour < 5% des lésions Surélévation minime possible par rapport au niveau de la peau normale
2	Léger	Plaques de coloration rouge Squames fines et minces Surélévation légère mais certaine par rapport au niveau de la peau normale
3	Moyen	Plaques de coloration rouge marquée Grosses squames Surélévation moyenne de plaques aux bords arrondis ou pentus
4	Sévère	Plaques de coloration rouge très foncée Grosses squames épaisses Surélévation marquée de plaques aux bords durs et tranchants
5	Très sévère	Plaques de coloration rouge très foncée à brun foncé Grosses squames épaisses, tenaces, très sévères Surélévation marquée de plaques aux bords durs et tranchants

Ó Richard MA. Psoriasis : bilan préthérapeutique pratique. *Ann Dermatol Venereol* 2011;138:813-20.

2. Localisation difficile à traiter : Ongle

f-PGA: Fingernail Physician's Global Assessment

Le psoriasis des ongles sera évalué à l'aide d'une échelle PGA en 5 points. Veuillez choisir le score global selon le score le plus élevé attribué.

Score	Category	Nail Bed Signs	Nail Matrix Sign
0	Clear	Onycholysis: Consistent with normal nail AND Hyperkeratosis: none AND Splinter Hemorrhages: Consistent with non-psoriatic splinter hemorrhages AND Nail Bed Erythema: none	No non-psoriatic nail plate irregularities including pitting, crumbling, Beau's lines, senile onychorrhexis and non-psoriatic leukonychia
	Minimal	Onycholysis: <10% involved on all nails OR Hyperkeratosis: present, but barely detectable elevation of nail plate OR Nail Bed Erythema: faint AND Splinter Hemorrhages: consistent with non-psoriatic splinter hemorrhages	No more than 5 pits or psoriatic leukonychia on any nail AND No crumbling
2	Mild	Onycholysis: >10% on five or more nails OR Hyperkeratosis: present with mild elevation of nail plate OR Splinter Hemorrhages: present on four or fewer nails OR Nail Bed Erythema: mild	5 or more nails with mild pitting (eg, >10 pits/nail) or psoriatic leukonychia AND No crumbling
3	Moderate	Onycholysis: >30% on five or more nails OR Hyperkeratosis: present with moderate elevation of nail plate OR Splinter Hemorrhages: scattered and present on five or more nails OR Nail Bed Erythema: moderate	5 or more nails with moderate pitting (eg, >25 pits/nail) AND ≤25% crumbling on any nails
4	Severe	Onycholysis: >50% on at least one nail OR Hyperkeratosis: present with severe elevation of nail plate OR Splinter Hemorrhages: numerous and present on five or more nails OR Nail Bed Erythema: severe	5 or more nails with severe pitting (>50 pits/nails) OR >25% crumbling on any nail

Ó Adapté à partir de Hudgens S, Rich P, Geng Z, Williams D, Fleischer A, Ganguli A. Development and validation of the Physician's Global Assessment of Fingernail Psoriasis. Published online May 20, 2021. J Eur Acad Dermatol Venereol. doi:10.1111/jdv.17387

3. Localisation difficile à traiter : Cuir chevelu

Scalp PGA: Scalp Physician's Global Assessment

Le ScPGA est une mesure de l'implication globale du cuir chevelu par l'investigateur au moment de l'évaluation à l'aide une échelle à 5 points et intégrant une évaluation de la sévérité des trois principaux signes de la maladie : érythème, desquamation et élévation de la plaque.

Lors de l'évaluation de la gravité globale du cuir chevelu, l'investigateur doit tenir compte des zones qui ont déjà été traitées et ne pas se contenter d'évaluer la gravité des lésions restantes. En cas de différences de gravité entre les signes du psoriasis, le signe qui est la caractéristique prédominante du psoriasis doit être utilisé pour aider à déterminer le score ScPGA

Score	Category	Description
0	Absence of disease	No evidence of redness, no evidence of thickness, and no evidence of scaliness on the scalp
1	Very mild disease	The overall clinical picture consists of flat lesions with barely perceptible erythema, with or without a trace of overlying fine scale
2	Mild disease	The overall clinical picture consists of lesions with mild erythema, slight, but define, thickness, and a thin scale layer
3	Moderate disease	The overall clinical picture consists of lesions with moderate erythema, a moderate thickness, and a moderate scaled layer
4	Severe disease	The overall clinical picture consists of lesions with bright erythema, severe thickness, and a severe, coarse thick scale layer

4. Localisation difficile à traiter : Palmoplantaire

PP-PGA : Palmoplantar PGA

Le psoriasis palmoplantaire sera évalué à l'aide d'une échelle PGA à 5 points. Veuillez choisir la catégorie qui représente le mieux l'état de la zone palmo-plantaire.

Score	Category	Description
0	Clear	No signs of plaque psoriasis
1	Almost Clear	Just perceptible erythema and just perceptible scaling
2	Mild	Light pink erythema, with minimal scaling with or without pustules
3	Moderate	Dull red, clearly distinguishable erythema with diffuse scaling, some thickening of the skin, with or without fissures, with or without pustule formation
4	Severe	Deep, dark red erythema with obvious and diffuse scaling and thickening as well as numerous fissures with or without pustule formation

5. Localisation difficile à traiter : Génital

sPGA-G: Static PGA of genitalia

Le sPGA-G est la détermination par l'investigateur de la gravité globale des lésions de psoriasis du patient dans la région génitale (grandes lèvres, petites lèvres et périnée chez la femme ; pénis, scrotum et périnée chez l'homme) à un moment donné. Dans l'ensemble, les lésions sont classées en fonction des descriptions de l'élévation, de l'érythème et de la desquamation. Il n'est pas nécessaire que les trois critères soient remplis. L'érythème étant le résultat le plus robuste, il devrait être la caractéristique dominante influençant le score sPGA des organes génitaux dans la majorité des cas, l'élévation des plaques et/ou la desquamation sont des caractéristiques secondaires.

Score	Category	Description
0	Clear	Erythema: residual or no erythema Plaque elevation: no elevation Scaling: no scale
1	Minimal	Erythema: faint, light pink erythema Plaque elevation: elevation is very slight and difficult to confirm Scaling: some fine, white surface dryness
2	Mild	Erythema: mild, pink erythema Plaque elevation: slight elevation with sloped edges Scaling: fine scale on some or most lesions
3	Moderate	Erythema: moderate, red erythema Plaque elevation: moderate elevation with sloped edges Scaling: coarse scale on most lesions
4	Severe	Erythema: severe, bright red erythema Plaque elevation: substantial elevation, hard or sharp edges Scaling: coarse, non-adherent scale on most to all lesions
5	Very Severe	Erythema: very severe, deep red erythema Plaque elevation: very significant elevation with hard and sharp edges Scaling: very coarse, thick, and adherent scale completely or nearly completely covering most of all lesions

© Eli Lilly and Company. Merola JF, Bleakman AP, Gottlieb AB, et al. The Static Physician's Global Assessment of Genitalia: a clinical outcome measure of the severity of genital psoriasis. *J Drugs Dermatol JDD*. 2017;16(8):793–9.

Annexe II – Auto-questionnaires

1. Auto-questionnaire sur la qualité de vie en Dermatologie (DLQI)

Ce questionnaire a pour but d'évaluer l'influence de votre problème de peau sur votre vie au cours des 7 derniers jours. Merci de compléter le questionnaire en ne cochant qu'une seule case par question.

1.	Au cours des 7 derniers jours, votre peau vous a-t-elle démangé(e), fait souffrir ou brûlé(e) ?	☐ Énormément ☐ Beaucoup ☐ Un peu ☐ Pas du tout	
2.	Au cours des 7 derniers jours, vous êtes-vous senti(e) gêné(e) ou complexé(e) par votre problème de peau ?	☐ Énormément ☐ Beaucoup ☐ Un peu ☐ Pas du tout	
3.	Au cours des 7 derniers jours, votre problème de peau vous a-t-il gêné(e) pour faire des courses , vous occuper de votre maison ou pour jardiner ?	☐ Énormément ☐ Beaucoup ☐ Un peu ☐ Pas du tout	☐ Non concerné(e)
4.	Au cours des 7 derniers jours, votre problème de peau vous a-t-il influencé(e) dans le choix des vêtements que vous portiez ?	☐ Énormément ☐ Beaucoup ☐ Un peu ☐ Pas du tout	☐ Non concerné(e)
5.	Au cours des 7 derniers jours, votre problème de peau a-t-il affecté vos activités avec les autres ou vos loisirs ?	☐ Énormément ☐ Beaucoup ☐ Un peu ☐ Pas du tout	☐ Non concerné(e)

6.	Au cours des 7 derniers jours, avez-vous eu du mal à faire du sport à cause de votre problème de peau ?	☐ Énormément ☐ Beaucoup ☐ Un peu ☐ Pas du tout	☐ Non concerné(e)
7a.	Au cours des 7 derniers jours, votre problème de peau vous a-t-il complètement empêché(e) de travailler ou d' étudier ?	☐ Oui ☐ Non	☐ Non concerné(e)
7b.	Si la réponse est "non" : au cours des 7 derniers jours, votre problème de peau vous a-t-il gêné(e) dans votre travail ou dans vos études ?	☐ Beaucoup ☐ Un peu ☐ Pas du tout	☐ Non concerné(e)
8.	Au cours des 7 derniers jours, votre problème de peau a-t-il rendu difficiles vos relations avec votre conjoint(e) , vos amis proches ou votre famille ?	☐ Énormément ☐ Beaucoup ☐ Un peu ☐ Pas du tout	☐ Non concerné(e)
9.	Au cours des 7 derniers jours, votre problème de peau a-t-il rendu votre vie sexuelle difficile ?	☐ Énormément ☐ Beaucoup ☐ Un peu ☐ Pas du tout	☐ Non concerné(e)
10.	Au cours des 7 derniers jours, le traitement que vous utilisez pour votre peau a-t-il été un problème, par exemple en prenant trop de votre temps ou en salissant votre maison ?	☐ Énormément ☐ Beaucoup ☐ Un peu ☐ Pas du tout	☐ Non concerné(e)

Ó A.Y. Finlay, G.K. Khan, avril 1992. Dermatology Life Quality Index (DLQI)

2. Auto-questionnaire sur le bien-être (WHO-5)

Veillez entourer pour chacune des cinq affirmations, laquelle se rapproche le plus de ce que vous avez ressenti au cours des deux dernières semaines. Notez que le chiffre est proportionnel au bien-être. Veillez ne sélectionner qu'une seule case par question

Au cours des 2 dernières semaines	<i>Tout le temps</i>	<i>La plupart du temps</i>	<i>La moitié du temps</i>	<i>Moins de la moitié du temps</i>	<i>De temps en temps</i>	<i>Jamais</i>
1. Je me suis senti(e) bien et de bonne humeur	5	4	3	2	1	0
2. Je me suis senti(e) calme et tranquille	5	4	3	2	1	0
3. Je me suis senti(e) plein(e) d'énergie et vigoureux(se)	5	4	3	2	1	0
4. Je me suis réveillé(e) en me sentant frais(che) et dispos(e)	5	4	3	2	1	0
5. Ma vie quotidienne a été remplie de choses intéressantes	5	4	3	2	1	0

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3.Questionnaire d'observance au traitement

Depuis la dernière visite :

2.1 Avez-vous réalisé l'injection de votre traitement conformément à la prescription de votre médecin ? ☐Oui ☐Non

2.2 Concernant la prise de votre traitement, avez-vous rencontré les difficultés suivantes

Oubli ou retard de l'injection ☐Oui ☐Non

Difficulté lors de l'injection ☐Oui ☐Non

Difficulté à respecter les modalités de conservation du traitement ☐Oui ☐Non

Autre, préciser SVP :
.....
.....

4. Questionnaire d'évaluation de l'activité physique

1. Pratiquez-vous une activité physique régulière ? ☐ Oui ☐ Non

Si oui, préciser la durée hebdomadaire en heures :heures/ semaine

2. En moyenne, combien d'heures par jour restez-vous assis ?heures/ jour
