RWE Study Protocol

ENSTILAR RWE STUDY, IN FRENCH EMR DATABASE (THIN®)

Drug utilization of Enstilar® and/or Daivobet® in real life settings, in patients diagnosed with psoriasis. A study using THIN® France, an ambulatory Electronic Medical Records database to characterize patient's profile and treatment patterns

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2. List of Abbreviations

ADR: Adverse Drug Reaction

AE: Adverse Event

BD: Bethametasone Dipropionate

CAL: Calciprotriene

CIP : Code Identifiant de Présentation (Presentation Identifier Code)

CNIL: Commission Nationale de l'Informatique et des Libertés

CNAM : Caisse Nationale d'Assurance Maladie

CRF: Case Report Form

CRO: Contract Research Organization

GPs: General Practioners

GRPD: General Regulation on Data Protection

HRi: History of Reimbursement integrated

HRU: Health Resource Use

IEC: Independent Ethics Committee

IRB: Institutional Review Board

LEO LEO Pharma A/S and/or affiliates or representatives

NIS: Non-Interventional Study

OE: Other Experience

PP: Plaque Psoriasis

QoL: Quality of Life

SAP: Statistical Analysis Plan

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4. Abstract

Title: Drug utilization of Enstilar® and/or Daivobet® in real life settings, in patients diagnosed with psoriasis. A study using THIN® France, an ambulatory Electronic Medical Records database to characterize patient's profile and treatment patterns

Rationale and background: Psoriasis is one of the most frequent occurring chronic inflammatory skin disorders that require long-term treatment. Severity of psoriasis is defined by different indicators, and about 20% to 30% of patients have moderate-to-severe disease[1,2], with the remaining patients having mild-to-moderate disease. There is a wide range of therapies available for the treatment of psoriasis, including topicals and systemics. Topical therapies are considered as first-line treatments for patients with psoriasis[3]. Calcipotriol/betamethasone (Cal/BD) combinations have been shown to be more effective than a placebo, calcipotriol or betamethasone alone[4-6] in clinical trials, and are indicated and reimbursed in France for treatment of psoriasis vulgaris in adults. Enstilar® foam formulation has shown superior efficacy than the ointment and gel formulation (Daivobet®) in phase II and phase III trials[7-10]. While, recent real-life data has led to suggest that Enstilar® as a benefit as therapy in "beyond-

mild" patients, little is known on real-life utilization in France. In addition, few data are available in terms of patient characteristics that trigger the prescription of Enstilar®, compared to other topical calcipotriol/ betamethasone fixed dose combinations in gel or ointment (Daivobet®).

Research question and objectives The research aim of this project is to better understand the utilization of Enstilar®, compared to Daivobet®, according to patient profile and treatment pathway and outcomes. A second objective is to characterize the Enstilar® prescription for "beyond mild" patients in France. This translates into a primary objective being to describe and compare profiles of patients who received Enstilar® and/or Daivobet®. The secondary objective is to describe, through a follow-up period, the treatment pathway and health resource utilization (HRU) for patients prescribed Enstilar® compared to Daivobet®. Then, exploratory objectives are to ob

Study design: the study is an observational, longitudinal, multicentric, retrospective and prospective cohort study on treatment patterns and characteristics within real-world setting of psoriasis patients who received Enstilar® and/or Daivobet® in France between April 2018 and May 2022.

Population Patients over 18, managed between April 1, 2018, and May 31, 2022 by physicians (GPs and dermatologists) part of the Cegedim's THIN® observatory, with an identified diagnostic of psoriasis. Patients are included in the cohort at their first delivery of Enstilar® and/or Daivobet® during the study period. Those included before December 31, 2021 will be described at inclusion time according to the treatment. Among them, longitudinal description of clinical evolution, healthcare pathway and treatments, will be realized when 18 months of follow-up is available. The strata of patients with "beyond-mild" psoriasis and who are under Enstilar® will be described. A complementary prospective study (through an additional questionnaire implemented in the EMR software) will be performed between February 10, 2022 and June 10, 2022 to complete the assessment of severity of the disease, understand the prescription characteristics and its impact on the quality of life.

Variables To describe and analyze patient management, demographic variables (age, gender) and medical data including physical examination data (height, weight, BMI), diagnoses (medical history / comorbidities), drug prescriptions, medical procedures and prescriptions will be collected. Reimbursement data for medical and paramedical procedures, including hospital outpatient consultations (dates), specialist referrals, hospitalizations, sick leave compensations and drug deliveries will also be used to assess the management of patients included in the cohort. Additional variables will be collected through the implemented formulary on a sample of patients, including: Psoriasis percentage of body area, location of psoriasis, impact on quality

of life, which are not otherwise routinely collected in the database. Those additional variables aim to assess a severity degree of the psoriasis in patients'life as well as the utilization of the subsequent treatments which would be utilized to identify patients with "beyond-mild" psoriasis.

Data sources Study data are collected from the French THIN® database, a longitudinal observational database, compliant with the GDPR. THIN® data are based on electronic medical records from general practitioners and office-based specialists, and integrates the CNAM[1] reimbursement history for patients in the panel.

Study size Due to study having 2 part:one being retrospective and the other one prospective, study size will be presented as samples size per objective. The enrollment figures below were calculated for the period for April 1, 2018 to September 30, 2021 and do not take into account the prospective elements. 10,350 patients cases are eligible (7,609 for the Daivobet® cohort and 2,741 for the Enstilar® cohort). Among these patients, 4,140 (3,214 for the Daivobet® cohort and 926 for the Enstilar® cohort) have already had 18 months of follow-up, making it possible to describe their healthcare pathway and treatments. Finally, 226 patients initiated on Enstilar® and meeting the markers of "beyond-mild" are identified. With enrollment through December 31, 2021, and use of the data through May 31, 2022, to assess the patient journey,. Data collection via the additional formulary will be done prospectively between February 10, 2022 and May 31, 2022. Based on current numbers and form response rates from previous studies, we estimate an average of 1,338 patients over a rolling 4-month period throughout 2022 and an estimated 40% of questionnaires completed and analyzable 500 patients' cases are foresee to be analyzed. the numbers currently observed are expected to increase.

Data analysis Patients' characteristics (including demographic characteristics, comorbidities and concomitant treatment) at inclusion will be compared between patients being under Enstilar® versus Daivobet®. Summary statistics (mean, median, SD, quartile, 3rd quartile, range for continuous variables and number of patients and percentages) will be calculated overall and per treatment group. Univariate comparisons will be performed using Chi-square (or Fisher) test and Student (or Wilcoxon) test as appropriate according to the class of the variable of interest.

For the follow-up cohort study, first, descriptive analyses of HRU and treatment patterns will be carried out in the two groups (Enstilar® versus Daivobet®). Second, time to switch to other psoriasis treatment in the two groups will be described using Kaplan Meier curve and compared using propensity score method to adjust on differences observed at baseline (delivery of Enstilar® of Daivobet®).

[1] CNAM : 93% of the population is insured by CNAM, which finances 90% of all health insurance expenditures.

For patients who received Enstilar® and who are included in the "beyond-mild" segment, summary statistics of patient characteristics at inclusion; HRU and treatment patterns during the follow-up period will be reported.

The percentage of psoriasis on the body surface, the location of psoriasis and the impact on quality of life of patients included in the prospective cohort will be described overall and compared according to the treatment. This analysis will be replicated in "beyond-mild" patients.

5. Amendments and Updates

None

6. Milestones

Milestone	**Planned Date**
Protocol – Version 1	Mid-October 2021
Board – Questionnaire validation	November 29, 2021
Board – Protocol: objectives validation	December 13, 2021
Protocol (including SAP) – Finale version validated by LEO	March 22, 2022
Start of data collection	April 1, 2018
End of data collection	May 31, 2022
Start of additional form data collection	February 10, 2022
End of additional form data collection	May 31, 2022
Final statistical report	June 30, 2022
Study report V1	July 31, 2022
Study report feedback by LEO	August 31, 2022
Final study report	September 14, 2022

7. Rationale and Background

Psoriasis is one of the most frequent occurring chronic inflammatory skin disorders that require long-term treatment. In western Europe, the prevalence of psoriasis has been estimated to 1.92% (1.07% to 3.46%) of adults[1]. Psoriasis vulgaris, also known as plaque psoriasis (PP), is the most frequent clinical form of psoriasis accounting for 80% to 90% of all psoriasis cases[2]. PP is characterized by sharply demarcated erythrosquamous plaques covered by white or silvery scales. Plaques vary in their extent and location, most commonly occurring on the elbows, knees, genitals, scalp, lower back, and buttocks and are often distributed symmetrically[2,3].

Plaques can be associated with pruritus and pain, as well as severe social stigmatization all the more pronounced as the lesions are visible or located on sensitive areas[4]. These manifestations are associated with anxiety, depression and significant impairment of patients' quality of life (QoL) shown to be equal and greater than that of diabetes, ischemic heart disease, or chronic obstructive pulmonary disease. Psoriasis is a chronic condition in more than 90% of cases[7], resulting in significant cumulative life course impairment for patients with persistent or relapsing symptoms.

Severity of the disease is partly defined by the body surface area (BSA) affected by plaques, or the Psoriasis Area Severity Index (PASI) that is more precise than BSA as it takes into account not only BSA but also the intensity redness, scaling and thickness of the plaque. Severity of psoriasis is also defined by its impact on the patient's quality of life, that can be assessed using the dermatology life quality index (DLQI)[8]. French guidelines define moderate-to-severe disease as psoriasis covering over 10% of the body surface area, or resulting in a PASI score >10 and/or a DLQI score >10[9]. About 20% to 30% of patients with psoriasis have moderate-to-severe disease[10,11], with the remaining patients having mild-to-moderate disease.

There is a wide range of therapies available for the treatment of psoriasis, both topical and systemic. Topical therapies include a wide range of agents such as vitamin D3 analogs, steroids, or dithranol. A Cochrane meta-analysis has confirmed the efficacy of these treatments in improving symptoms[12]. These therapies can be given as monotherapies or as combinations.

Calcipotriol/betamethasone (Cal/BD) combination has been shown to be more effective than a placebo, calcipotriol or betamethasone alone[12-14] and is indicated for psoriasis vulgaris in France. Enstilar® is a topical fixed-dose of calcipotriol/ bethametasone combination as an aerosol foam that enables supersaturation of Cal/BD greatly enhancing skin penetration and bioavailability. Enstilar® foam formulation has shown superior efficacy than the ointment and gel formulation (Daivobet®) in phase II and phase III trials[15-18]. Both treatments, Enstilar® and

Daivobet® are indicated and reimbursed in France in the topical treatment of psoriasis vulgaris in adults.

Topical therapies are considered a first-line treatment for patients with mild-to-moderated disease[19], In the case of moderate to severe stages, other therapeutic options are considered, first non-biological systemic treatments (including phototherapy, apremilast, ciclosporin and methotrexate), then biological therapies if the response is not yet achieved. While the more severe patients rely on systemic therapy to control their psoriasis, there is question on how patients between mild and severe stage ("beyond-mild") can be treated by and benefit from topical or systemic therapies or both combined. In a population-based multinational assessment of psoriasis treatment practices, physician reported that 74.9% of patients with moderate-to-severe psoriasis were also receiving topical therapy [20].

In patients with disease severity between mild and severe, described under the concept of "beyond-mild" psoriasis[21], Enstilar® was shown to be as effective treatment as in mild patients[22-25]. This has been confirmed in observational studies, with Enstilar® being used for beyond-mild patients in real-life. [21,26] This has led to consider Enstilar® as a potential alternative as monotherapy or as an add-on treatment to non-biologic or biologic systemic therapy in "beyond-mild" patients[27].

While these practices have been described in real-life settings in Germany, the UK, Spain or Greece [21,26,28], there are no data, describing Enstilar® utilization in real-life condition in France.

8. Research Question and Objectives

Little is known in France on real-life utilization characteristics of Enstilar®, in particular in terms of patients profile.

The research aim of this study is to better understand the utilization of Enstilar®, compared to Daivobet®, according to patient profile, treatment pathway, and evolution and to characterize the Enstilar® prescription for "beyond-mild" patients in France.

This translates into the following primary objective :

- to describe and compare profiles of patients who received Enstilar® and/or Daivobet®,

The secondary objective includes:

- to describe through an 18 months follow-up period, treatment pathway and health resource utilization (HRU) for patients prescribed with Enstilar® compared to Daivobet®.

Exploratory objectives include:

- to characterize profile of patients with "beyond-mild" psoriasis and under Enstilar®, to assess how they are prescribed with Enstilar® and to describe their follow-up
- to better describe psoriasis severity and its impact on quality of life for patients under Enstilar® and/or Daivobet®.

9. Research Methods

9.1 Study Design

This study is an observational, longitudinal, multicentric, retrospective and prospective cohort study on treatment patterns and characteristics within real-world setting of psoriasis patients who received Enstilar® and/or Daivobet® in France between April 1, 2018 and May 31, 2022.

This non-interventional study will conform to the European Directive 2001/20/EC [29], and will follow the HAS guidelines for real-life studies and ENCePP 2018 checklist.

9.2Setting

9.2.1 Data source

This study will use the THIN® France database, which is a quality, controlled longitudinal ambulatory-care database that contains routinely collected medical data, prescriptions and reimbursement data from a panel of physicians including general practitioner (GP) and dermatologists, since 1994. These practitioners have been selected to be representative of the global practitioner cohort in terms of gender, age and geographic locations. Physicians have the possibility to access the past 12 months of reimbursements/claims of patients (any products delivered, any medical acts including hospitalization) through a social security service for the management of their patients. All the prescriptions made by these practitioners are paired with a corresponding prescription diagnosis.

In addition, formularies can be set up and deployed on the physician's software to collect further information on a prescription/disease condition, that is not automatically recorded in the

patient's file, or poorly collected. In this study, a formulary will be deployed between February 10, and June 10, 2022, to collect additional information including: psoriasis severity stage, impact on quality of life, and location of psoriasis that is not otherwise collected.

9.2.2 Index date

The index date for the retrospective cohort is the date of the first delivery of Enstilar® or Daivobet® without any CAL/BD delivery in the previous 30 days during the inclusion period (cf. below). For the prospective cohort, the index date is the first prescription of Enstilar® or Daivobet® during the inclusion period (cf. below). This index date will be derived from delivery data for retrospective cohort and prescription data for prospective cohort.

9.2.3 Study periods

9.2.3.1 Inclusion period

Two inclusion periods are defined:

1- The retrospective cohort includes patients from THIN® France database between April 1, 2018 and December 31, 2021

2- The prospective cohort includes patients from THIN® France database between February 10, 2022 and May 31, 2022

9.2.3.2 Historical period

For the retrospective cohort, the total historical period is between January 1, 1994 and March 31, 2018. This period is necessary to:

- ensure that patients included are not new in the panel
- derive the comorbidities recorded during the full history before the index date
- identify patients with concomitant treatment during the three months before the index date
- ensure that patients included within the first month before the index date had no delivery of Enstilar® or Daivobet®.

For the prospective cohort, the historical period is between January 11, 2022 and February 10, 2022. This period is necessary to:

- ensure that patients included are not new in the panel

9.2.3.3 Follow-up period

Only patients included in the retrospective cohort will be followed during 18 months. Thus, the period will be run from the index date to the index date + 540 days.

Patients included in the prospective cohort will not have period of follow-up.

9.2.4 Study population

Patients recorded in the THIN® France database who meet all the inclusion/non inclusion criteria declined by objectives below.

9.2.4.1 Inclusion criteria:

1. Patient aged 18 years or more
2. Followed by a panelist physician, GPs or Dermatologists, from the THIN® France database
3. With at least one record of psoriasis diagnosis in their electronic file *(ICD10 : L40.0, L40.1, L40.3, L40.8, L40.9)*
4. Who received Enstilar® and/or Daivobet® between April 1, 2018 and May 31, 2022

The treatment received by the patient will be determined by delivery data for the retrospective cohort and by prescription data for the prospective cohort (cf. below).

Additional inclusion criteria will be applied according to objectives:

- For the primary objective : to describe and compare profiles of patients who received Enstilar® or Daivobet®,
  5. the inclusion is determined by the first delivery of Enstilar® or Daivobet® without any CAL/BD delivery in the previous 30 days between April 1, 2018 and December 31, 2021

The treatment arm is defined by the first treatment received by the patient at inclusion. Patients who received both treatments on the index date are expected to be low. If this number is more than 30, patients will be described but excluded from comparative analyzes.

- For the secondary objective: to describe, through a follow-up period, the treatment pathway and health resource utilization (HRU) for patients prescribed Enstilar® compared to Daivobet®,
  6. The patients included previously and with 18 months of follow-up available after the index date

- For the exploratory objective: to characterize profile of patients with "beyond-mild" psoriasis and under Enstilar®, to assess how they are prescribed with Enstilar® and to describe their follow-up
  7. Patients included previously in the Enstilar® arm AND classified as "beyond-mild"

  Patients will be classified as "beyond-mild" whether they meet one of the following criteria during the period defined between index date - 90 days and index date + 540 days:

Within the study population, patients with specific treatments:

- *Systemic conventional treatments : phototherapy, methotrexate, ciclosporin, acitretin ;*
- *Or small molecules :apremilast;*
- *Or anti‑TNF alpha (infliximab, etanercept, adalimumab, certolizumab), Anti‑IL12/23 (ustekinumab), Anti‑IL17 (secukinumab, brodalumab, Ixekizumab), Anti‑IL23 (tildrakizumab, guselkumab, risankizumab);*
- *Or high consumption of Enstilar®, ie. more than 12 units dispensed over a rolling 3-month period.*
- *Or high consumption of Daivobet®, ie. more than 12 units dispensed over a rolling 3-month period.*
- *Or high consumption of Enstilar® and Daivobet®, ie. more than 12 cumulative units of the 2 treatments delivered over a 3-month rolling period.*

- For the exploratory objective: to better describe psoriasis severity and its impact on quality of life for patients under Enstilar® and/or Daivobet®.
  8. The inclusion is determined by the first prescription of Enstilar® and/or Daivobet® during a consultation with a panelist physician, GPs or Dermatologists, between February 10, 2022 and June 10, 2022, independently to their previous inclusion for retrospective cohort. In order to be included in the prospective study, only forms with answers to at least one of the following questions will be considered:
     a. Body surface area covered by psoriasis
     b. Impact on patient's quality of life
     c. Specific psoriasis location
     d. Intention to a systemic usage

9.2.4.2 Exclusion criteria:

Because the longitudinality of the data collected must be ensured, all patients meeting at least one of the following criteria will be excluded from the study population:

1. Patients with consultation history less than 3 months prior to inclusion
2. Patients without history reimbursement integrated (HRi) between the 75th and the 105th days before inclusion
3. Patients without any consultation at 3 months or more after inclusion

For the follow-up cohorts:

4. Patients without complete reimbursement history during the 18 months of follow-up

9.2.5 Data collection

For patients included retrospectively, all data recorded in THIN® France database from 1994 up to February 2022 will be extracted. For patients included prospectively, some data will be collected prospectively from the THIN® France database until study completion in May 2022.

The prospective data collection, in addition to routinely collected medical charts and prescriptions data, will include a specific questionnaire (cf. Annex 3. Questionnaire for prospective collection data) on patients prescribed with Enstilar® or Daivobet® to characterize the severity of their diagnosis and quality of life elements. The questionnaire will be submitted to the physician during the patients' routine follow-up visits to collect these additional information (Section 9.3).

Data collection overview – detail of the different categories is listed in the tab below:

	Retrospective cohort		Prospective cohort
	At inclusion	At follow-up	At inclusion
Sociodemographic characteristics	X		X
Psoriasis Disease History (disease duration…)	X		X
History of psoriasis associated comorbidities	X		X
Health resource used (visit specialists, hospitalizations…)		X	
Prior Psoriasis treatments prescriptions and dispensations	X		X
Enstilar® or Daivobet® prescriptions and dispensations	X	X	X

Subsequent Psoriasis treatments prescriptions and dispensation		X	
Concomitant prescriptions and dispensation	X	X	X
Disease severity assessed by physician			X
Patients Quality of Life assessed by physician			X

9.3 Variables

All variables will be derived from the THIN® France database. The ICD-10 codes, acts codes and CIP codes used in this study are summarized in the appendix (cf. Annex 2. Codes for identification of variables in THIN.). The treatment variables will be derived from reimboursement history tables.

9.3.1 Variables of patients selections

Some of the following variables will be derived two times, the first time for the retrospective cohort and the second time for the prospective cohort.

Inclusion variables

- Adult patients (aged 18 and more) with at least one record of psoriasis diagnosis (cf. Annex 2. Codes for identification of variables in THIN.) and who received Enstilar® and/or Daivobet® between April 1, 2018 and December 31, 2021 for the retrospective cohort, or between February 10, 2022 to May 31, 2022 for the prospective cohort.
- Patients followed by GPs from the THIN® France database (binary variable as Yes/No);
- Patients followed by Dermatologists from the THIN® France database (binary variable as Yes/No);
- Patients without any CAL/BD delivery during the 30 days prior to the index date derived as binary variable (Yes/No);
- Patients who received Enstilar® at index date (Yes/No). This variable will be derived using the delivery table for retrospective cohort and the prescription table prospective cohort;
- ICD10 Psoriasis codes : each code will be derived as binary variable using full history recorded before index date (Yes/No)

- Patients who received Enstilar® and who are in "beyond-mild" segment defined in the

section cf. 9.2.4.1 for the patients included in the retrospective cohort or as BSA >10 for the patient included in the prospective cohort.

- Non inclusion criteria (specific to the restrospective cohort except the last condition listed)

    - Patient with consultation history less than 3 months prior to inclusion (Yes/No)
    - Patient without history reimbursement integrated (HRi) available between the 75th and the 105th days before to index date (Yes/No)
    - Patient without any consultation 3 months or more after index date (Yes/No)
    - Patients who received Enstilar® and Daivobet® at index date (binary variable as Yes/No);
    - Patients without complete reimbursement history during the 18 months of follow-up (Yes/No).

9.3.2 Variables of the groups and subgroups

- Treatment groups : among included patients, two groups of patients will be derived for each cohort (retrospective and prospective) according to the first treatment (Enstilar® or Daivobet®) they received during the inclusion period

- Treatment subgroups will be derived only for patients included in the retrospective cohort: among patients who have been initated with Enstilar® and who are in the "beyond-mild" segment (variables of the patients who received Enstilar® and who are in "beyond-mild" equal to Yes), subgroups will be derived based on their treatment combination with Enstilar® at index date $-$ 90 days and index_date + 540 days.The closest concomitant therapy to the first delivery of Enstilar® will define the subgroup to which the patient is allocated. This variable will have these categories:

    - Enstilar® monotherapy with more than 12 units dispensed over a rolling 3-month period
    - Enstilar® + Methotrexate
    - Enstilar® + Other conventionnal systemics (Ciclosporin / Acitretin)
    - Enstilar® + Apremilast
    - Enstilar® + Anti-TNF
    - Enstilar® + Anti-Interleukin
    - Enstilar® + Phototherapy

Subgroups of patients with numbers <30 patients will be grouped.

Even if the patients switch during the follow-up period, the patients will remain in the initial classification.

9.3.3 Variables for the primary objective: Patient characteristics

Patient characteristics will be derived for all those included in the retrospective cohort on the index date or within ±90 days of the index date :

Sociodemographic characteristics at index date:

- Age in years : difference between index date and July 1, year of birth in days/365.25
- Gender (male, female)
- Body Mass Index (BMI)
- Specialty of the panel physician to whom the patient is related (GP/dermatologist)

Psoriasis Disease History at index date:

- Duration of psoriasis in years: continue variable calculated from the date of the first diagnosis of psoriasis recorded in the database to the index date
- Beyond-mild at index date (Yes/No). The proxy is used to identify patients beyond-mild between index date - 90 days and index date + 90 days
- Duration of beyond-mild classification in months and years since the index date : continue variable calculated between the date of the beyond-mild classification and the index date.

Concomitant treatment variables: Patients who received the specific treatment at least once within ± 90 days of the index date will be coded as Yes, otherwise as No :

- Topical treatments prescribed: (Vitamin D3 analogs, Steroids Dithranol)
- Phototherapy
- Methotrexate
- Other systemic conventional treatments (ciclosporin, acitretin)
- Small molecules (Apremilast)
- Anti-TNF alpha (Infliximab, Etanercept, Adalimumab, Certolizumab)
- Anti-IL12/23 (Ustekinumab)
- Anti-IL17 (Secukinumab, Brodalumab, Ixekizumab)
- Anti-IL23 (Tildrakizumab, Guselkumab, Risankizumab)

History of psoriasis associated comorbidities (each comorbidity will be coded as binary variable Yes/No)

- Psoriatic Arthritis (all patients with ICD10: L40.5)
- Metabolic Syndrome (ICD10: E88)

- Dyslipidemia (ICD10: E78.5)
- Cardiovascular Diseases (ICD10: I20-I25, I48, I50, I63-I66, I70, I71, I73)
- Obesity (ICD10: E66)
- Hypertension (ICD10: I10)
- Inflammatory Bowel Disease (ICD10: K50-K52)
- Diabetes (ICD10: E10-E14)
- Chronic Obstructive Pulmonary Disease (ICD10: J44)
- Depression (ICD10: F32-F33)
- Sleep disorders not due to a substance or known physiological condition (ICD10: G47)
- Suicide attempt (ICD10: R45.8)

- Drugs coprescribed with psoriasis treatments : (ATC4)

Differential diagnostic of psoriasis[30] : each of the following comorbidities will be derived first as binary variable of patients who have at least one diagnose of interest (Yes/No) and second as continueous variables which represent the history duration of the disease in months at index date since the date of the first record of the diagnose of interest :

- seborrheic dermatitis
- Tinea capitis
- tinea corporislichen planopilaris in the scalp
- lupus erythematosus
- dermatomyositis
- cutaneous T-cell lymphomas
- atopic dermatitis
- eczema
- syphilis psoriasiform
- pityriasis rubra pilaris in the trunk and arms
- pemphigus
- infectious intertrigo in the inguinal and intergluteal folds
- palmoplantar keratoderma in the palms and soles

9.3.4 Variables of the secondary objective: Treatment pathway and health resource utilization during the follow up

For all patients included in the retrospective cohort and who have a follow-up of at least 18 months after their index date, the following variables will be derived.

Health Resource Utilization (HRU) available in reimbursement history tables during the 18 months of follow-up:

- Patients who have undergone at least one GP visit (Yes/No)
- Number of GP visits per patient (continuous variable)
- Patients who have undergone at least one Dermatologist visit (Yes/No)
- Number of Dermatologist visits per patient (continuous variable)
- Patients who have undergone at least one Rheumatologist visit (Yes/No)
- Number of Rheumatologist visits per patient (continuous variable)
- Patients who have undergone at least one Endocrinologist visit (Yes/No)
- Number of Endocrinologist visits per patient (continuous variable)
- Patients who have undergone at least one hospitalization (Yes/No)
- Number of hospitalization visits per patient (continuous variable)
- Patients who have at least one sick leave compensations (Yes/No)
- Total time of sick leave per patients (continuous variable)

Treatment patterns variables :

- Patient with a discontinuation of treatment received at index date (Enstilar® or Daivobet®) as binary variable (Yes/No)
- Time to discontinuation in months since index date of Enstilar® or Daivobet® as continuous variable (Yes/No)

A discontinuation of treatment is defined as no delivery of any psoriasis treatment during a period of at least 6 months. As there is no evidence on the adequate period of discontinuation, a sensitivity analysis will be conducted with a discontinuation redefined as no delivery of any psoriasis treatment during a period of at least 9 months.

- Patients who switch to another psoriasis treatment (any topic treatment other than the initial treatment, systemic or biologic treatment) as binary variable (Yes/No)
- Time to switch to another psoriasis treatment in months since index date
- Patients who switch from Daivobet® to Enstilar® as binary variable (Yes/No)
- Time to switch from Daivobet® to Enstilar® in months since index date

- Treatment intensification: switch to a systemic or a biologic treatment as binary variable (Yes/No).
- Time to treatment intensification in months since index date

Of note , for the Daivobet® arm, the dispensation of its generics will not be considered as a switch to another topical.

- Quantity of Enstilar® delivered in pharmacy within the 18 months after index date
- Quantity of Daivobet® delivered in pharmacy within the 18 months after index date
- The following treatments or classes of treatment will be derived at each line (1st line to n line) of treatments from the first delivery of Enstilar® or Daivobet® (index date) to the end of follow-up or discontinuation. The sequence of treatment for each included patient will be calculated from the date of the delivery of the first (or subsequent) treatment to the date of the the next subsequent treatment delivered (or the date of the end of the follow-up for the last treatment delivered during the follow-up):
    - Enstilar® or Daivobet®
    - Class of treatments (cf. 9.3.1 for the list of treatments in each class)
        - Topical treatments prescribed
        - Methotrexate
        - Phototherapy
        - Other conventional systemics (Ciclosporin, Acitretin)
        - Apremilast
        - Anti-TNF alpha
        - Anti-IL12/23
        - Anti-IL17
        - Anti-IL23

<u>For survival analyses: time-to-event outcome recorded during the follow-up</u>:

- Time to switch to another psoriasis treatment[2] (others topic than the initial treatment, systemic or biologic teatment) or discontinuation (see above the definition) is calculated by the absolut difference between the date of the next treatment (after the initation of Enstilar® or Daivobet®) delivered or discontinuation and the index date +1 day

[2] Delivery of another psoriasis treatment in addition to the initiated treatment (Enstilar® or Daivobet®) will not be considered as switch.

- The event will be a switch to another psoriasis treatment (other topics than the treatment at index date, systemic or biologic treatment) or a discontinuation (see above the definition)
- The patient is censored if at the end of the follow-up he did not switch to another psoriasis treatment or has not stopped treatment.

9.3.5 Variables of the exploratory objective : to characterize profile of patients with "beyond-mild" psoriasisand under Enstilar® and to describe their follow-up

This section includes the following derived variables on the retrospective cohort of Enstilar® introduced patients who are in the "beyond-mild" segment.

- Characteristic of patient variables (cf. 9.3.3)
- Patients becoming "beyond-mild" during the follow-up (Yes/No)
- For patients becoming "beyond-mild" during the follow up: month (from 0 to 18 months) of classification as beyond-mild. Thus identified before during the history period will be coded as 0 month.
- HRU variables, treatment patterns variables (cf. 9.3.4)

9.3.6 Variables of the exploratory objective : to better describe psoriasis severity and its impact on quality of life for patients under Enstilar® and/or Daivobet®

The following variables will be obtained from an additionnal questionnaire on patients under Enstilar®, that will be submitted to the physician during the patients' routine follow-up visits:

- Length of psoriasis disease (categorical variable)
- Body surface area covered with psoriasis expressed in number of hands (continuous variable)
- Consequence of psoriasis on the patient's quality of life assessed by his physician (Yes/No)
- Specific location of psoriasis (categorical variable)
- Joint pain (Yes/No)
  - If Yes, length of joint pain (categorical variable)
- Coprescription of a systemic treatment (Yes/No)
  - If No, intention to prescribe a systemic (Yes/No)
- Intention to refer the patient at a physician specialist (Dermatologist and/or Rheumatologist) (categorical variable)

9.4Data Source

Study data to be collected from the THIN® France database.

The THIN® France database is a longitudinal observational database established in 1994. The THIN® France database contains the anonymized electronic patient records of 2,401 GPs and 28 dermatologists (private practice exclusively). These practitioners meet standard criteria regarding the quality of data entry: they have been selected to be representative of the global practitioner cohort in terms of gender, age and geographic locations.

The records consist of demographic (age, sex) and medical data including physical examination data (height, weight, blood pressure), diagnoses, drug prescriptions, laboratory test and medical procedures prescriptions and results, as well as reimbursement data for medical and paramedical procedures, including hospital outpatient consultations, specialist referrals, and hospitalizations, and drug delivery.

Each patient has a unique identification number associated with a THIN® France panel physician. All diagnoses are coded according to the International Classification of Diseases, tenth revision, Clinical Modification (ICD-10-CM). Drug prescriptions comprised information on trade names, formulations, and active substances, and are encoded with Anatomic Therapeutic Chemical (ATC) classification.

Although the data are mainly collected via the panel of general practitioners, no bias on data collection should be observed due to the selected inclusion and exclusion criteria. To be included in the population, patients must have integrated reimbursement history information, which allows their dispensations to be collected from retail pharmacies, regardless of who prescribed the treatment, during the entire study period. All dispensations will be collected: Enstilar® and/or Daivobet® as well as any other treatments.

9.5Study Size

The study is aimed to describe all patients being under Enstilar® or Daivobet® and met inclusion criteria (cf. 9.2.3.4) will include all elibigle patients in the THIN® France database.

Because one part of the study is retrospective and the other prospective, the size of the study is presented below considering the available enrollment at the end of December 2021.The enrollment figures below were calculated for the period between April 1st, 2018 to September 30th, 2021 and do not take into account the prospective elements. 10,350 patients cases are eligible (7,609 for the Daivobet® cohort and 2,741 for the Enstilar® cohort) to describe the patient profile that will be analyzed in the primary objective of the study.

Among these 10,350 patients, 4,140 (3,214 for the Daivobet® cohort and 926 for the Enstilar® cohort) have already had 18 months of follow-up, making it possible to describe their healthcare pathway and treatments. Finally, 226 patients being under Enstilar® and meeting the markers of "beyond-mild" are identified. With enrollment through December 31, 2021, and use of the data through May 31, 2022, to assess the patient journey, the numbers currently observed are expected to increase.

Data collection via the additional formulary will be done prospectively between February 10, 2022 and May 31, 2022. Based on current numbers and form response rates from previous studies, we estimate an average of 1,338 patients over a rolling 4-month period throughout 2022 and an estimated 40% of questionnaires completed and exploitable, 500 patients cases are foresee to be analyzed.

9.6 Data quality process and data management

THIN® database collates the computerized medical records of general practitioners (2,401 GPs) and specialists office-based (1,000 specialists) in France. These practitioners have been selected to be representative of the global practitioner cohort in terms of gender, age and geographic locations. Physicians have the possibility at each consultation to access the past 12 months of reimbursements/claims of patients (any products delivered, any medical acts including hospitalization) through a social security service for the management of their patients. All the prescriptions made by these practitioners are paired with a corresponding prescription diagnosis.

THIN® stands for The Health Improvement Network. Data is collected at the physicians' level through Electronic Health Records in an unobtrusive, fully GDPR-compliant way, and is anonymized at source.

9.6.1 THIN® Quality Process

Data collection is conducted locally in Franceand then transmitted to the Cegedim Headquarter who centralizes and validates each dataset according to a standardized process. The process has been set up by Cegedim to ensure quantitative and qualitative quality controls throughout the data chain from data transmission by physician until integration into the datalake.

A team of dedicated data managers is in charge of this part via an internal applications developed on the purpose of data validation and quality control. An audit trail is available in the tool and used to improve continuously the quality.

This process allows an on-going follow-up of the transmissions and of the transmitted values.

Data validation relies on three pillars:

1. Number of physicians transmitting each month
2. Volume of data transmitted
3. Quality of data transmitted

Data volume and quality validation include more than 100 automatic control queries. There is an assisted validation using two dynamic on-line tools:

- Health Data Oberver to monitor transmission quality
- Health Data Lab for quantitative analysis of the data.

In addition, ad hoc control queries are developed when necessary.

The validations are made on prescriptions, number of contacts, dispensing data, vaccination, physicians, diagnoses, and other variables. The whole process is run on a monthly basis.

The process for data quality control takes place in 2 phases:

a) Data transmission and integration (check if data was transmitted and integrated as expected):

   Daily controls are automatically performed on the data volume integrated in the database on all criteria: contacts, prescriptions and detail prescriptions, acts, exams, diagnoses, new patients, measures, biologic information and others criteria. When data are rejected, a specific control of each field is implemented to identify the reason of the reject and provide the adequate correction. Alerts threshold for anomalies detection have been defined, enabling alerts creation with details. Each anomaly is assigned for resolution. Reason for alerts includes: too many rejections, duration of treatment too long, unknown patient_id, unknown physician_id, outlier posology data and many other cases.

b) Data Analysis and quality check:

   The automatic quality checks include structure of the data (formats, …), detection of new data (drugs, vaccines, patients, physicians, …). Alerts appear when some nonconformity appears. Advanced validation then checks for data representativeness (prevalence, number of contacts, detection and investigation of potentially abnormal peaks and patterns (eg: seasonality, acute situations such as Covid-19 related,) are made. Automatic validation is made on a monthly basis, and ad-hoc quality control is made on

a quarterly basis. The automatic validation is coded and is automatic whenever a new month of historic data is added and processed. Connection to SQL Microsoft Server and data extraction are done using R software version 4.1.2 or later.

9.6.2 Data management for this study

The THIN® data needed to carry out this study will not follow the usual process of extracting and importing data for analysis to avoid format issues when importing files. To ensure the reproducibility of the data management of this study, a generic program developed in the R software will be used to connect directly to the Microsoft SQL server and prepare the data for the analyzes. A program specific to this study will be developed to identify outliers, check them and discuss them with the medical director before excluding them if necessary. Abnormal values, for example, of weight are not excluded at the full database level. Quality checks of the computer program will be performed to ensure reproducibility of the data preparation.

9.7Data Analysis

9.7.1 General consideration

Statistical analysis will be carried out using R 4.0.0 software of upper version.The numeric variables will be described by mean ± standard deviation, median, interquartile range (1st quartile, 3rd quartile), minium and maximum. The categorical variables will be described by numbers of patients and proportions. The denominator of the proportions will not include the number of missing data. However the number of missing data will be reported. No method to impute missing data will not applied.

Comparisons between two groups will be carried out using appropriate statistical tests:

- The numerical variables will be comparad using the Student test (or Wilcoxon rank test);
- The categorical variables will be donne using the Chisquare test without Yates' correction (or Fisher exact test)

Comparison will be considered as statistically significant if the p-value is less than 0.05.

As the objective of the study is to describe the psoriasis patients (who have intiated Enstilar® or Daivobet®) in real-life, no method will be used to hundel for multiplicity tests. Calculated results with numbers less than 30 patients will not be reported.

Population analyses sets

As the population of the analyses differ according to the objectives, the following sets have been defined.

- For the retrospective cohort:
    - **Primary objective set (=Full Set)**: Patients introducing Enstilar® or Daivobet®
    - **Longitudinal Set**: Patients being under on either Enstilar® or Daivobet® with at least 18 months of follow-up data after index date
    - **Longitudinal Enstilar "Beyond-mild" Set**: Patients who received Enstilar® with severity greater than mild (cf definition) and at least 18 months of follow-up data after index date.

- For the prospective cohort:
    - **Prospective Set**: Patients with a consultation with a physician from THIN® France panel between February 10, and May 31, 2022 and prescribed Enstilar® or Daivobet® during this consultation.

9.7.2 Planned analysis for patients selection:

The number of patients included will be described step by step from the application of the first criteria to the last inclusion/non inclusion criteria. The results will be summarized following the Shell Table 1 (for the retrosrespective cohort) and the Shell Table 2 (for the prospective cohort)

Table 1: Patient selection for the retroprospective cohort

Selection Criteria	**Overall (N=XXX)**
Adult patients (aged 18 or more) and with at least one record of psoriasis diagnosis recorded in THIN® France database and with a first delivery of Enstilar® or Daivobet® without any CAL/BD delivery during the previous 30 days between April 1, 2018 and December 31, 2021	xxxx
Patients who met the above criteria and belonging to the panel of GPs or Dermatologists of THIN® France database: Patients included by Dermatologists Patients included by GPs	xxxx xx (p %) xx (100 - p %)
Patients who met the above criteria with at least one consultation history 3 months before the index date	xxxx
Patients who met the above criteria and without any consultation 3 months after index date	xxxx
Patients who met the above criteria without co-delivery on the same day of Enstilar® and Daivobet®	xxxx
Patients who met all inclusion/non inclusion criteria : Included patients under Enstilar® Included patients under Daivobet®	xxxx xxxx (p %) xxxx (100 - p %)
Included patients with a complete reimboursement history during the 18 months of follow-up : Patients under Enstilar® and with at least 18 months of follow-up Patients under Daivobet® and with at least 18 months of follow-up	xxxx xxxx (p %) xxxx (100 - p %)
Included patients under Enstilar® who have a complete reimboursement history during the 18 months of follow-up and are in “Beyond-mild” segment	xxxx

No. : number of patients. GP: General Practioner. (1) between April 1, 2018 and December 31, 2021

***Table 2**: Patient selection for the prospective cohort*

Selection Criteria	**Overall (N=XXX)**
Adult patients (aged 18 or more) with at least one record of psoriasis diagnosis and belonging to the panel of GPs or Dermatologists of THIN® France database and who have a prescription of Enstilar® or Daivobet® between February 10, 2022 and May 31, 2022	xxxx
Patients who met the above criteria with at least one consultation history 3 months before the index date and included in the prospective cohort	xxxx
Patients who met the above criteria and who have at least one question filled on the questionary	xxxx
Patients who met the above criteria and whose pop-up questionary are answered at all the following questions will be considered: a. Body surface area covered by psoriasis b. Impact on patient's quality of life c. Specific psoriasis location d. Intention to a systemic usage	xxxx
Patients who are included in prospective cohort and are in "Beyond-mild" segment	xxxx

No. : number of patients.

9.7.3 Planned analysis for the primary objective: Patient characteristics

For primary objective analysis, the Primary Objective Set will be used. This analysis will include all variables derived in the section 9.3.3. Summary statistics of this variables will be presented overall and by treatment groups (Enstilar® vs Daivobet®). For categorical variables (e.g., sex) frequencies and percentages will be presented. The denominator for the percentages will be the number of patients with non-missing data. For continuous variables (e.g., age) number of non-missing values, mean, median, standard deviation (SD), first quartile (Q1), third quartile (Q3) and range will be presented. Characteristics of patients included in the Enstilar® and Daivobet® groups will be compared using Student T-test (or Wilcoxon rank test) for continuous variables and Pearson chi-square test (or exact Fisher test) for proportions. The results will be reported following the Shell table, Table 3

***Table 3**: Characteristic of patients under Enstilar® or Daivobet®*

	Overall (N=XXX)	**Enstilar® (N=XXX)**	**Daivobet® (N=XXX)**	**P**
Age				
N	xxxx	xxxx	Xxxx	

	Overall (N=XXX)	**Enstilar® (N=XXX)**	**Daivobet® (N=XXX)**	**P**
Mean ± SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	0.xxx
Median (q1, q3)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
min, max	xx, xx	xx, xx	xx, xx	
Missing	xx	xx	Xx	
Gender, no. (%)				
Female	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	0.xxx
Male	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	
BMI				
N	xxxx	xxxx	Xxxx	
Mean ± SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	0.xxx
Median (q1, q3)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
min, max	xx, xx	xx, xx	xx, xx	
Missing	xx	xx	Xx	
...				
Comorbidities				
Psoriatic Arthritis				
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	0.xxx
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	
…	…	…	…	
Concomitant treatments				
Vitamin D3 analogs				
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	0.xxx
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	
…				
Anti-IL23				
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	0.xxx
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	

N: Number of patients. BMI: Body Mass Index. SD: Standard Deviation.

9.7.4 Planned analysis for the secondary objective: Treatment pathway and health resource utilization during the follow up

The following analyses will be done on Longitudinal Set: Patients being under Enstilar® or Daivobet® with at least 18 months of follow-up data after theirindex date.

Health resource analyses:

Summary statistics (mean, median, SD, quartile, 3rd quartile, range for continuous variables or number of patients and percentages for categorical variables) will be calculated for all HRU variables (cf. 9.3.4) overall and per treatment group. Results will be reported following the Shell Table 4.

***Table 4**: Health resource used during the 18 months follow-up period*

	Overall (N=XXX)	**Enstilar® (N=XXX)**	**Daivobet® (N=XXX)**	**P**
At least one GP visit, no. (%)				
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	0.xxx
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	
Number of GP visits per patient				
N	xxxx	xxxx	xxxx	
Mean ± SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	0.xxx
Median (q1, q3)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
min, max	xx, xx	xx, xx	xx, xx	
….				
At least one sick leave				
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	0.xxx
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	
Total duration of sick leave per patient				
N	xxxx	xxxx	xxxx	
Mean ± SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	0.xxx
Median (q1, q3)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
min, max	xx, xx	xx, xx	xx, xx	
Missing	xx	xx	xx	

N: Number of patients. SD: Standard Deviation.

Treatment patterns analyses:

Several analyses will be carried out to describe the treatment patterns of the Enstilar® and Daivobet® groups:

- First, summary statistics of psoriasis treatment, presented in section 9.3.4, will be reported in the two treatment groups (see Shell Table 5)
- Second, number and percentage of patients for each treatment sequence will be reported (see Shell Table 6).
- Third, number and percentage of patients who have received each class of psoriasis treatment at each line (from the 2nd to the 5thline) will be presented, (see Shell tables 7 to 10)
- Finally, for each treatment group, a sunburst diagram will be generated to summarize, in an interactive figure, all sequences of psoriasis treatment class delivered during the follow-up, see Figure 1.

Table 5*: Psoriasis treatment during 18 months follow up*

	Overall (N=XXX)	**Enstilar® (N=XXX)**	**Daivobet® (N=XXX)**
Patient with a discontinuation of initial treatment (Enstilar® or Daivobet®)			
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Time to discontinuation in months since initial of Enstilar® or Daivobet®			
Mean ± SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Median (q1, q3)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
min, max	xx, xx	xx, xx	xx, xx
Patients who switch to others psoriasis (others topic than the initial treatment, systemic or biologic teatemnt)			
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
…			
Time to treatment intensification in months since the initial of Enstilar® or Daivobet®			
Mean ± SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Median (q1, q3)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
min, max	xx, xx	xx, xx	xx, xx
…			
At least one systemic conventional, no. (%)			

	Overall (N=XXX)	**Enstilar® (N=XXX)**	**Daivobet® (N=XXX)**
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
At least one methotrexate, no. (%)			
Yes			
No			
Number of methotrexate delivery per patients			
N	xxxx	xxxx	xxxx
Mean ± SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Median (q1, q3)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
min, max	xx, xx	xx, xx	xx, xx
…			
At least one Anti-IL17, no. (%)			
Yes			
No			
Number of methotrexate delevery per patients			
N	xxxx	xxxx	xxxx
Mean ± SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Median (q1, q3)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
min, max	xx, xx	xx, xx	xx, xx

No.: Number of patients. SD: Standard Deviation.

Table 6*: Sequence treatment during the 18 months follow-up period*

	Enstilar® (N=XXX)	**Daivobet® (N=XXX)**
Sequences, no. (%)		
Other topic-Systemic-Biologic-Enstilar	xxx (xx.x)	xxx (xx.x)
Other topic-Systemic-Daivobet-Biologic	xxx (xx.x)	xxx (xx.x)
…	xxx (xx.x)	xxx (xx.x)
Systemic-Daivobet-Enstilar	xxx (xx.x)	xxx (xx.x)
Biologic-Daivobet-Enstilar	xxx (xx.x)	xxx (xx.x)

No.: Number of patients.

***Table 7**: Class of psoriasis treatment delivered at the second line*

	Enstilar® (N=XXX)	**Daivobet® (N=XXX)**
Sequences, no. (%)		
Other topic	xxx (xx.x)	xxx (xx.x)
Daivobet	xxx (xx.x)	-
Enstilar	-	xxx (xx.x)
…	xxx (xx.x)	xxx (xx.x)
Systemic Daivobet	xxx (xx.x)	xxx (xx.x)
Biologic Daivobet	xxx (xx.x)	xxx (xx.x)

No.: Number of patients among patients who have received at least one treatment in second line;

***Table 8**: Class of psoriasis treatment delivered at the third line*

***Table 9**: Class of psoriasis treatment delivered at the fourth line*

***Table 10**: Class of psoriasis treatment delivered at the fifth line*

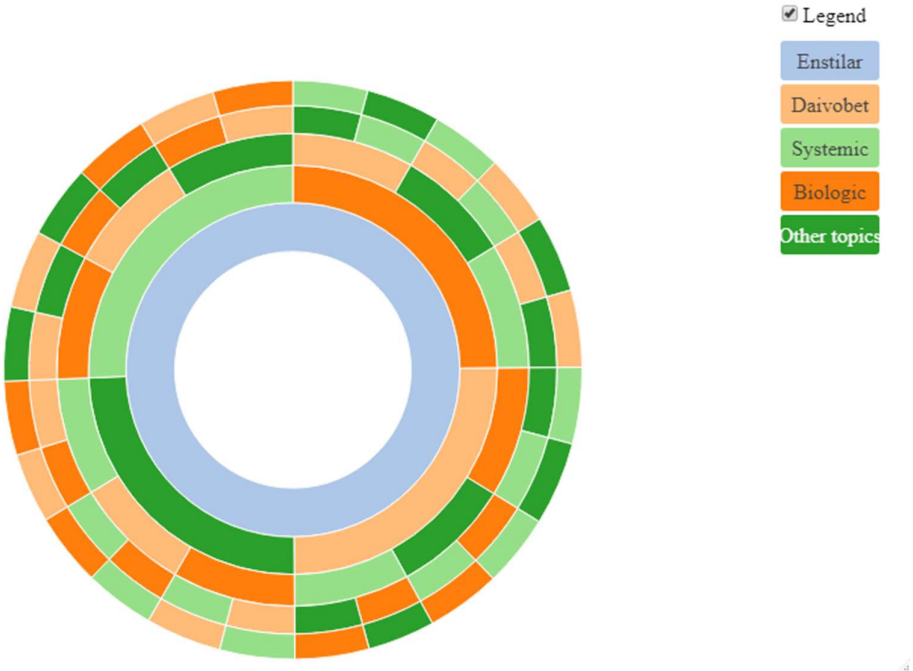

***Figure 11**: Sunburst of treatment sequences following the first delivery of Enstilar® .*

This figure was made from simulated data.

Time to discontinuation or switch analyses:

Time-to-event analysis will include descriptive analyses per each 4 months in the two groups of patients (Enstilar® or Diabobet®). Two events are defined as the switch to other psoriasis treatment or discontinuation after the first deliveryof Enstilar® or Daivobet®.
Number and pourcentage of patients per event ; number of patients at risk ; and Kaplan Meier probability of free of event will reported following the Shell table, Table 6 and figure 2

Table 11*: Switch to other psoriasis treatment or discontinuation after the first delivery of Enstilar® or Daivobet®*

	Main analysis Discontinuation defined as at least 6 months without delivery of psoriasis treatment		**Sensitivity analysis Discontinuation defined as at least 9 months without delivery of psoriasis treatment**	
	Enstilar® (N=XXX)	**Daivobet® (N=XXX)**	**Enstilar® (N=XXX)**	**Daivobet® (N=XXX)**
Patient per event (who switch(1)), no. (%)				
4th month	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
8th month	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
…	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Patients at risk to switch (1), no. (%)				
4th month	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
8th month	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
…				
KM probability of free to switch (1), no. (%)				
4th month	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
8th month	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
4th month	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

No.: Number of patients in the full dataset. SD: Standard Deviation. (1) Switch or discontinuation

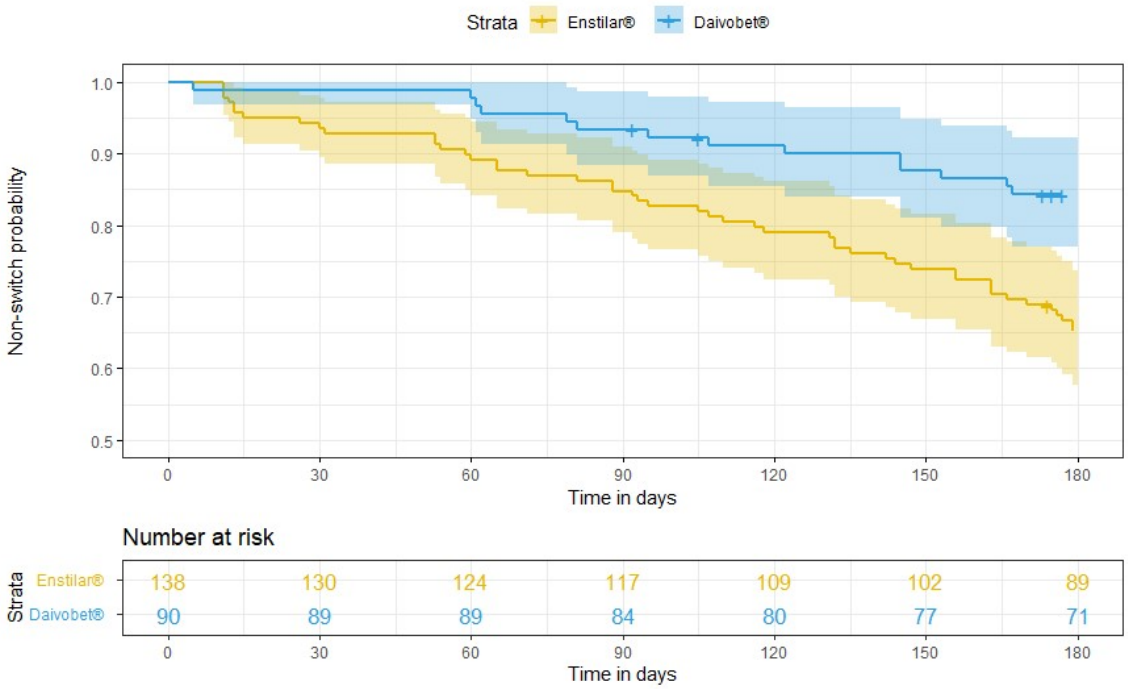

***Figure2 2**: Kaplan Meier of non-switch curve carried out on the full data set*

This figure was made from simulated data.

In addition, an **exploratory analysis will be done** to compare the two treatment groups (Enstilar® vs Daivobet®) on an outcome time to event defined as the switch from (Enstilar® or Daivobet®) to other psoriasis treatment (cf. section 9.7.4) or discontinuation .

Adjustments for Indication Bias

The study is a nonintervention design. Therefore, treatments are not attributed at random and they may exist differences in baseline characteristics between patients initiating Enstilar® or Daivobet® leading to an indication bias. To minimize this potential bias, statistical models will be adjusted for imbalances found at baseline using propensity scores.

First, the propensity score will focus on differences between patients' characteristics at treatment index date, which will range from patient demographics, previous medications and comorbidities. Covariates with more than 10% of the patients missing covariates, likely including disease severity, will be excluded from the propensity score. The propensity score will be derived from logistic regression model including the treatment group variable (Enstilar®

or Daivobet®) as dependent variable and the selected covariates (reviewed and validated by expert comittee) as independent variable. Interaction terms may be included.

Second, the overlap of the scores will be assessed by visual inspection, and depending on the overlap the propensity scores will be used as a covariate; to match each patient being under Enstilar® to the nearest neighbor patient being under Daivobet®.

Finally, the comparison will be done on the matched dataset if sample size allows it or using other methods like inverse probability weighting.

After adjustement for confounding, the results will be presented following the Shell tables, Table 12 and figure 3. Unadjusted Hazard (HR) ratio calculated on the full dataset and Adjusted HR estimated on the matched dataset will be presented, see Table Shell 13.

***Table 12**: Switch to other psoriasis treatment or discontinuation after the first delivery of Enstilar® or Daivobet® and after adjustment for confounding factors*

	Main analysis Discontinuation defined as at least 6 months without delivery of psoriasis treatment		**Sensitivity analysis Discontinuation defined as at least 9 months without delivery of psoriasis treatment**	
	Enstilar® (N=XXX)	**Daivobet® (N=XXX)**	**Enstilar® (N=XXX)**	**Daivobet® (N=XXX)**
Patient per event (who switch(1)), no. (%)				
4th month	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
8th month	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
…	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Patients at risk to switch (1), no. (%)				
4th month	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
8th month	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
…				
KM probability of free to switch (1), no. (%)				
4th month	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
8th month	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
4th month	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

No.: Number of patients in the matched dataset . SD: Standard Deviation. (1) Switch or discontinuation

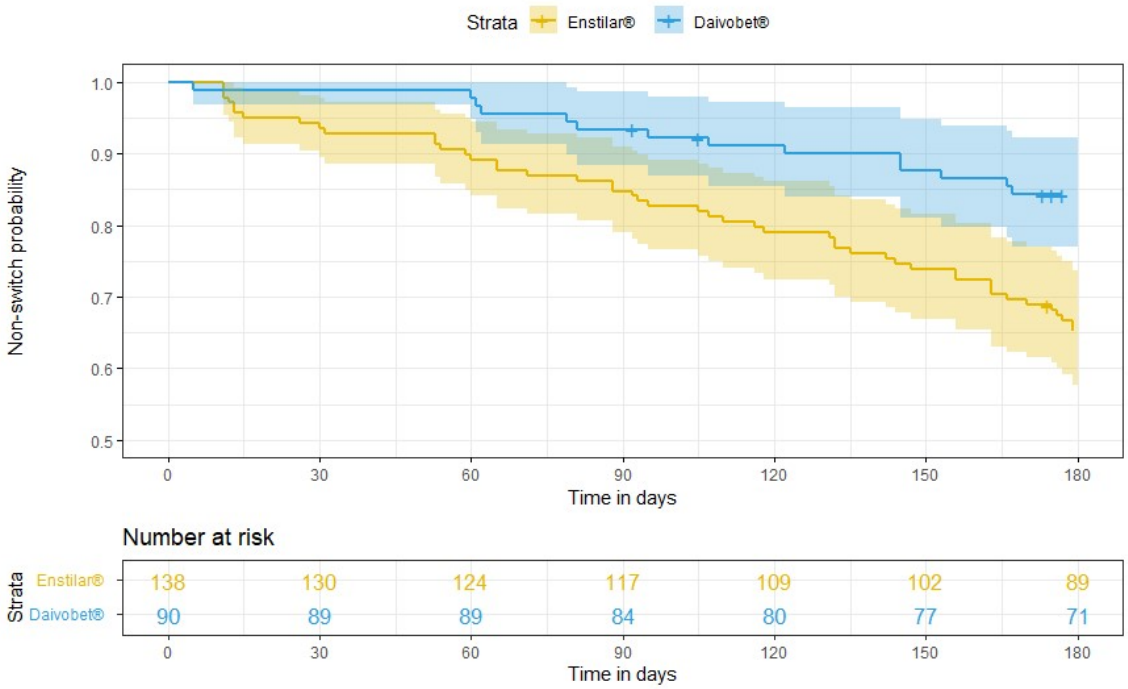

***Figure3 3**: Kaplan Meier of non-switch curve carried out on the matched data set*

This figure was made from simulated data.

***Table 13**: Hazard ratio of Switch to other psoriasis treatment or discontinuation after the first delivery of Enstilar® or Daivobet®*

	Full dataset (N= XXX)		Mached dataset (N= XXX)	
	Unadjusted HR (95% CI)	**P**	**Adjusted HR (95% CI)**	**P**
Main ananlysis [(1)]				
Enstilar vs Daibobet	X.XX(1)	0.xxx	X.XX[(1)]	0.xxx
Sensitivity analysis				
Enstilar vs Daibobet[(2)]	X.XX	0.xxx	X.XX[(2)]	0.xxx

CI: Confidence Interval.
[(1)]Defined as no delivery of any psoriasis treatment during a period of at least 6 months
[(2)]defined as no delivery of any psoriasis treatment during a period of at least 9 months.

9.7.5 Planned analysis for objective 3: profile of beyond-mild patients under Enstilar®

These analyses will be carried out on Longitudinal-Enstilar-Beyond-mild Set. This part will be descriptive and will include all variables presented in the sections 9.3.5. For categorical variables number of patients and percentages will be presented. The denominator for the

percentages will be the number of patients with non-missing data. For continuous variables number of non-missing values, mean, median, standard deviation (SD), first quartile (Q1), third quartile (Q3) and range will be presented. Thus, except comparatives analyses, all previous analyses (figures and tables) will be repeated on subgroup of patients in beyond-mild-segment under Enstilar®.

In addition, time since the index date to the date of qualification in beyond-mild segment of patients will be described by Kaplan Meier curve

9.7.6 Planned analysis for objective 4 : describe psoriasis severity and its impact on quality of life for patients under Enstilar® and/or Daivobet®

Psoriasis percentage of body area, location of psoriasis and QoL outcomes (cf. 9.3.6) of patients included in the prospective cohort will be described overall and compared between the two treatment groups. In additon, this analysis will be replicated for patients in the beyond-mild segment.

***Table n-114**: Psoriasis severity and its impact on quality of life for patients for patients under Enstilar® and/or Daivobet®*

	Enstilar® (N=XXX)	**Daivobet® (N=XXX)**	**P**
Length of psoriasis disease			
Mean ± SD	xx.x ± xx.x	xx.x ± xx.x	0.xxx
Median (q1, q3)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
min, max	xx, xx	xx, xx	
Missing	xx	xx	
…			
Body surface area covered with psoriasis expressed in number of hands			
Mean ± SD	xx.x ± xx.x	xx.x ± xx.x	0.xxx
Median (q1, q3)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
min, max	xx, xx	xx, xx	
…			
Intention to prescribe a systemic			
Yes	xxx (xx.x)	xxx (xx.x)	0.xxx
No	xxx (xx.x)	xxx (xx.x)	
…			

No.: Number of patients. SD: Standard Deviation. (1) Switch or discontinuation

***Table n15**: Psoriasis severity and its impact on quality of life for patients for patients under Enstilar® and/or Daivobet® who are in beyond-mild segment*

	Enstilar® (N=XXX)	**Daivobet® (N=XXX)**	**P**
Length of psoriasis disease			
Mean ± SD	xx.x ± xx.x	xx.x ± xx.x	0.xxx
Median (q1, q3)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
min, max	xx, xx	xx, xx	
Missing	xx	xx	
…			
Body surface area covered with psoriasis expressed in number of hands			
Mean ± SD	xx.x ± xx.x	xx.x ± xx.x	0.xxx
Median (q1, q3)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
min, max	xx, xx	xx, xx	
…			
Intention to prescribe a systemic			
Yes	xxx (xx.x)	xxx (xx.x)	0.xxx
No	xxx (xx.x)	xxx (xx.x)	
…			

No.: Number of patients . SD: Standard Deviation.

9.8Limitations of Research Methods

This study is a noninterventional real-world study, where only routinely available data is available, and where treatment attribution was not made at random:

- Missing data are expected, in particular:
    - No disease severity index is expected to be collected routinely. Thus a specific questionnaire will be set up during the prospective phase to collect severity data at the prescription of Enstilar® or Daivobet®. However, in order to keep the most possible the observational design of the study, it is not compulsory for the doctors to fill in this additional formulary. Thus, a large proportion of patients treated with Enstilar® or Daivobet® during the prospective period will have missing data for severity.
    - Some demographic data and lab results : for example weight is missing for some patients in the THIN data base. However, in real world follow-up of patients, these data are usually missing when they are not relevant, as the physicians collect these data when the patient is overweight or the weight is a risk factor

for their comorbidities. In case the patient is healthy /with a "normal" weight, the physician will not collect the information routinely.

- Comorbidities: Physician may not collect all patient diagnoses at each visit. The THIN® France database has a long patient history (since 1994), the use of this complete patient history allows uswill allow to be the most exhaustive possible concerning the patients' comorbidities

- The bias of prescription by a GP or a dermatologist is covered by the utilization of the delivery of Enstilar® and Daivobet® in retail pharmacy; then the prescriptions by dermatologist or any other physicians not included in the THIN® France observatory will be considered.
- Potential indication bias between patients receiving Enstilar® and Daivobet® are expected that could be a cofounding factor for treatment duration comparison. Propensity scores will be used to reduce the risk associated with this bias, however, there will be limited availability of data to assess patient severity (see previously) that could be a potential important factor in treatment decision.
- No direct data will be available for observance, as dispensed medication does not necessarily indicate that the patient will actually use the medication as prescribed, which is expected to be an important factor in the real world. However, this bias should not be differential for comparative analyses between patients treated with Enstilar® or Daivobet® which are both topical treatments with an indication in psoriasis.

Audits and Inspections

The Quality Assurance (QA) unit at LEO may audit the study to ensure that study procedures comply with the protocol and LEO standard operating procedures, and that collected data is correct and complete.

Representatives from IRB/IEC or Competent Authority may in rare cases wish to inspect the study on site. Upon receiving notification of such inspection, the Study Site Responsible must immediately contact LEO and must make the records available as requested.

10 Protection of Human Subjects

All patients are informed by their panelist physician of the possibility of reusing their health data in an anonymized way and an information notice is given to them at the beginning of their follow-up. Patients can object to the collection of their data.

THIN® is a public health observatory with a legitimate interest that has existed for more than twenty years in France. The database is anonymized, respects the general regulation on data

protection (GRDP) and has been declared to the CNIL. As the patient record completion form is not interventional, no additional CNIL authorization is required for its implementation.

The recourse to a committee of protection of the persons is not necessary.

11 Management and Reporting of Adverse Events and Other Experiences

Not applicable.

Data collection is made through an anonymized EMR database. Adverse events are not recorded in such databases, nor patient are identified. Hence, no adverse event is expected to be collected for the retrospective part.

With regard to the prospective questionnaire to physicians, no safety question are part of the research. Both products are well established product and the study is not expected to yield any new safety data based on the research questions.

12 Plans for Disseminating and Communicating Study Results

Data and analyses will be integrated into a publication plan, targeting both local and global events and journals.

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Annex 1. List of Stand Alone Documents

There is no stand-alone document. All documents listed bellow are included in this protocol. The pointed 4 and 5 are not appropriate for such study.

Number	Document Reference number	Date	Title	
	None	None	Contact and responsibility details for all parties contributing to the study	Included in the protocol
2	None	None	Data Management Plan	Included in the protocol
3	None	None	Statistical Analysis Plan	Included in the protocol
4	None	None	Monitoring Plan	None
5	None	None	LEO Adverse Event Form – Marketed Products	None
6	None	None	Questionnaire for prospective collection data	Included in the protocol

Annex 2. Codes for identification of variables in THIN.

Annex 2_Codes for diagnoses and treatm

Annex 3. Questionnaire for prospective collection data

Psoriasis form.pdf