PASS Information

Title	An Observational Post-Authorisation Safety Study of Skilarence in European Psoriasis Registers
Protocol version identifier	*Version 1.2*
Date of last version of protocol	14 June 2018
EU PAS register number	Study will be registered prior to start of data collection.
Active substance	Dimethyl fumarate (ATC code: Not yet assigned)
Medicinal product	Skilarence® (dimethyl fumarate)
Product reference	EMEA/H/C/002157
Procedure number	Centralised Procedure No. EMEA/H/C/002157
Marketing authorisation holder(s)	Almirall S.A.
Joint PASS	No
Research question and objectives	This study aims to evaluate the long-term safety of Skilarence used for the treatment of patients with moderate to severe psoriasis. The study seeks to evaluate whether the use of Skilarence is associated with an increased risk of serious infections (including serious opportunistic infections such as progressive multifocal leukoencephalopathy [PML]), malignancies, or renal impairment as compared with conventional (non-biologic) systemic therapies. In addition, the study aims to describe the use of Skilarence in patient subgroups for which there is missing information, as identified in the Risk Management Plan.
Country(-ies) of study	Germany, Spain, United Kingdom, and Republic of Ireland
Author	Elena Rivero Ferrer, MD, MPH, FISPE, on behalf of the Skilarence PASS research team Director, Epidemiology RTI Health Solutions Diagonal 605, 9-1 08028 Barcelona, Spain

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Approval Page: RTI Health Solutions

Project Title: An Observational Post-Authorisation Safety Study of Skilarence in European Psoriasis Registers

Protocol ID Number: M-41008-40

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	Prof. Dr. Matthias Augustin (German Center for Health Services Research in Dermatology)
Version and Date:	Version 1.2, 14 June 2018

The following people have reviewed the protocol and give their approval:

[redacted]

14 JUN 2018
Date

Susana Perez-Gutthann, MD, MPH, PhD, FISPE, FPRC
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Approval Page: Almirall, S.A.

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The following people have reviewed the protocol and give their approval:

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German Kreis, MD, PhD Corporate Drug Safety Almirall, S.A.	*Date*

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2 List of Abbreviations

AE	adverse event
AESI	adverse events of special interest
Almirall	Almirall S.A.
BADBIR	British Association of Dermatologists Biological Interventions Register
BIOBADADERM	Spanish Register of Systemic Therapy in Psoriasis
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
DDD	defined daily dose
DMF	dimethyl fumarate
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FAE	fumaric acid esters
GPP	Guidelines for Good Pharmacoepidemiology Practices
GVP	Guideline on Good Pharmacovigilance Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRR	incidence rate ratio
ISPE	International Society for Pharmacoepidemiology
IVDP	Institute for Health Services Research in Dermatology and Nursing
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
PAS	post-authorisation study
PASS	post-authorisation safety study
PBRER	Periodic Benefit-Risk Evaluation Report
PML	progressive multifocal leukoencephalopathy
PRAC	Pharmacovigilance Risk Assessment Committee
PsoBest	German Register on the Treatment of Psoriasis With Biologics and Systemics
PUVA	psoralen plus ultraviolet A radiation
SAE	serious adverse event
SOC	system organ class
UK	United Kingdom

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Note: Following signature of collaboration agreements with Almirall, researchers from BADBIR, BIOBADADERM, and PsoBest have contributed to the review of this common protocol. Information from the registers included in this protocol is based on publicly available information or information provided by register custodians to the marketing authorisation holder.

4 Abstract

Title: An Observational Post-Authorisation Safety Study of Skilarence in European Psoriasis Registers

Rationale and background: Psoriasis is a chronic inflammatory skin disorder that results from complex interactions between genes, the immune system, and environmental factors, although the exact cause remains unclear. In Western countries, the estimated prevalence of psoriasis ranges from 2% to 4%, with a higher prevalence in northern countries, and this varies according to age. The relative frequency of moderate to severe psoriasis, which requires systemic treatment, has been reported to represent about 25% of all cases.

Skilarence is a gastroresistant tablet formulation of dimethyl fumarate (DMF) developed by Almirall S.A. (Almirall) for the treatment of moderate to severe chronic plaque psoriasis in adult patients in need of systemic therapy. The Skilarence pivotal phase 3 study 1102 showed that the safety profile of DMF alone was comparable to that of Fumaderm® (FAE). The main side effects observed were gastrointestinal symptoms and flushing, and other AEs occurred with similar frequency. There is a lack of data on the long-term safety of the Skilarence formulation of DMF, as well as safety in populations not included in the clinical trials. In November 2015, Almirall submitted to the European Medicines Agency (EMA), via a centralised procedure, the Marketing Authorisation Application (MAA) for Skilarence for the treatment of moderate to severe psoriasis, including the Risk Management Plan for Skilarence. The Committee for Medicinal Products for Human Use (CHMP) requested to obtain data on the long-term safety of Skilarence in the post-marketing setting, with a focus on safety concerns of interest (serious infections, malignancies, and all types of renal injuries). Specifically, Almirall was asked to explore different options for collecting these data and to consider the use of one or more psoriasis-specific patient registers to conduct a post-authorisation safety study (PASS).

This PASS will use data collected from patients with psoriasis enrolled in established psoriasis-specific registers of patients treated with systemic therapies. The study will evaluate populations covered in three registers of patients (one each in Germany and Spain, and one in the United Kingdom [UK] and the Republic of Ireland).

Research question and objectives: This study aims to evaluate the long-term safety of Skilarence used for the treatment of patients with moderate to severe psoriasis. The study seeks to evaluate whether the use of Skilarence is associated with an increased risk of serious infections (including serious opportunistic infections such as progressive multifocal leukoencephalopathy [PML]), malignancies, or renal impairment as compared with conventional (non-biologic) systemic therapies (hereafter, “conventional systemic therapies”). In addition, the study aims to describe the use of Skilarence, in particular in patient subgroups for which there is missing information in the Risk Management Plan.

The specific primary objectives are the following:

- To evaluate the risk of serious infections—overall, serious opportunistic infections, and PML individually—in new users of Skilarence compared with new users of conventional systemic therapies
- To evaluate the risk of malignancies in new users of Skilarence compared with new users of conventional systemic therapies

- To evaluate the risk of all types of renal impairment events (including Fanconi syndrome) in new users of Skilarence compared with new users of conventional systemic therapies
- To describe the characteristics of patients with psoriasis who initiate treatment with Skilarence and of patients with psoriasis who initiate treatment with conventional systemic therapies

The secondary objectives are the following:

- To evaluate the incidence of all "other" serious AEs (SAEs) (other than those covered by the primary objectives), by MedDRA* System Organ Class (SOC)
- To evaluate the incidence of all AEs by MedDRA SOC
- To evaluate safety data for the following special populations of patients with psoriasis treated with Skilarence: patients aged over 65 years; pregnant and lactating woman; patients with renal impairment, hepatic impairment, gastrointestinal disease, or preexisting infections; and immunosuppressed patients

Study design: Long-term, non-interventional, observational PASS that will use a prospective cohort design and data primarily collected in established registers of patients with psoriasis treated with systemic therapies in European countries. Data from the registers will be used to identify cohorts of patients with psoriasis who are new users of Skilarence or who initiate treatment with conventional systemic therapies. Conventional systemic therapies include oral psoralen plus ultraviolet A radiation (PUVA), methotrexate, ciclosporin, and oral retinoids (e.g., acitretin)—as included by each register. The study period will start on the date when Skilarence becomes available in each country and will end on 31 December 2026, allowing at least an 8-year period of enrolment. Patients will be characterised at baseline and followed from cohort entry through the end of the study period to determine the incidence of the safety concerns of interest.

Population: The source population will consist of patients with psoriasis who initiate treatment with a systemic therapy in regular clinical practice in selected European countries.

Patients will be eligible to enter in the study cohort if they meet the following criteria: have been diagnosed with psoriasis, have initiated treatment with Skilarence or a conventional systemic therapy, and have given consent to be enrolled in the selected established registers for psoriasis between the date that Skilarence became available in the selected country and the end of the study period.

Patients will be excluded if they are enrolled in a clinical trial or do not qualify for or do not give consent for enrolment in the register.

* MedDRA = Medical Dictionary for Regulatory Activities (http://www.meddra.org/).

Variables:

Safety endpoints

- Primary endpoints:
  - All serious infections
  - Serious opportunistic infections
  - PML
  - All malignancies
  - All renal impairments, including Fanconi syndrome
- Secondary endpoints:
  - All "other" SAEs
  - All AEs

Exposure

The main exposure of interest is treatment with Skilarence. The comparator will be conventional systemic therapies for psoriasis—oral psoralen plus ultraviolet A radiation (PUVA), methotrexate, ciclosporin, oral retinoids (e.g., acitretin), leflunomide, FAE—as included by each register. The following characteristics of exposure will be captured:

- Dose of Skilarence at treatment start and first maintenance dose, in three categories: above the recommended dose, below the recommended dose, and recommended dose
- Duration of treatment
- Discontinuation of treatment and reason(s)

Other variables

- Demographics: age, sex
- Body mass index, smoking status, and alcohol use, as available in each register
- Specific baseline comorbidities, including but not limited to renal, hepatic, and gastrointestinal diseases; preexisting infections; and immunosuppressive conditions at treatment start
- Comedications at baseline, including but not limited to immunosuppressants and nephrotoxic and hepatotoxic medications, as available in each register
- Previous systemic psoriasis therapy, where available
- Laboratory tests results (creatinine, transaminase [ALT]), where available
- Type of psoriasis, psoriatic arthritis, years since psoriasis diagnosis, percentage of body surface area with psoriasis lesions and Psoriasis Area Severity Index (PASI) score, physician global assessment (PGA) score, and Dermatology Life Quality Index (DLQI) score at treatment start, as available in each register

Data sources*: This study will use data primarily collected in established registers of patients with psoriasis treated with systemic therapies in European countries. The study is proposed to be conducted in the following countries and patient registers:

- Germany—the German Register on the Treatment of Psoriasis With Biologics and Systemics (PsoBest)
- Spain—the Spanish Register of Systemic Therapy in Psoriasis (BIOBADADERM)
- UK and Republic of Ireland—the British Association of Dermatologists Biological Interventions Register (BADBIR)

Study size: The study size will be driven by the uptake of Skilarence after product launch and reimbursement approval in each of the selected countries.

Germany and the UK are the two countries with the highest forecasted sales, followed by Spain, Italy, and Sweden. The defined daily dose (DDD) for Skilarence is 360 mg/day, and the dose needs to be adjusted individually to each patient. This complicates estimating the number of patients treated in each country from sales data.

There are no specific a priori hypotheses to be evaluated, but it is expected that patients in the Skilarence group will have similar incidence rates of serious infections, serious opportunistic infections, PML, malignancies, and all types of renal impairment as patients in the conventional systemic therapies group.

Assuming an incidence rate of serious infections of 0.77 per 100 person-years and a similar estimated incidence rate for all types of renal impairment events, 3,316 person-years of risk accumulated in the Skilarence cohort are required to detect an incidence rate ratio (IRR) of 2 for the comparison of Skilarence with conventional systemic therapies in the scenario of equal follow-up time in each group (1:1 person-time ratio). In the scenario with a person-time ratio of 1:2 (twice as much person-time at risk for the conventional systemic therapies cohort), 2,401 person-years of risk in the Skilarence cohort are required to detect the same IRR of 2.

Assuming an incidence rate of malignancies of 1.05 per 100 person-years, 2,443 person-years of risk accumulated in the Skilarence cohort are required to detect an IRR of 2 for the comparison of Skilarence with conventional systemic therapies in the scenario of equal follow-up time in each group (1:1 person-time ratio). In the scenario with a person-time ratio of 1:2 (Skilarence to conventional systemic therapies), 1,769 person-years of risk in the Skilarence cohort are required to detect the same IRR of 2.

Patient recruitment into the targeted registers will be monitored periodically and reported in the progress reports. If after 3 years from study start the number of patients in the targeted registers remains low, the inclusion of additional patient registers in other countries will be explored.

* Contacts with register custodians have been established. All expressed interest in participating in the study.

Data analysis: For each register, standard analysis will be run annually, covering the sections below and taking into account data availability and established register analytic templates. The analysis will be conducted at the routine fixed time points established by each register:

- Description of the study cohorts at baseline:
  - Demographics: age, sex
  - Specific baseline comorbidities at treatment start
  - Comedications at baseline, where available
  - Treatment for psoriasis prior to inclusion in the cohort
- Description of treatment course:
  - Number of patients and cumulative person-time of follow-up accrued in each study cohort
  - Number and percentage of patients who discontinued treatment in each cohort
  - Description of reasons for discontinuation
- Description of the safety endpoints (serious infections, serious opportunistic infections, PML, malignancies, all types of renal impairment) in each cohort, by MedDRA Preferred Terms and SOC:
  - Number of safety endpoints reported, number and percentage of patients with the safety endpoint, and cumulative patients with each type of event per 100 patient-years
- Description of all “other” SAEs and all AEs in each cohort, by MedDRA SOC

For each register, at the end of the study period, the following analyses will be conducted in addition to the analyses previously described, as is possible with the accrued number of patients and events:

- Description of the study cohorts at baseline using mean values and standard deviations for continuous variables and percentages for categorical variables:
  - Demographics: age, sex
  - Body mass index, smoking status, alcohol use
  - Specific baseline comorbidities at treatment start
  - Comedications at baseline, where available
  - Previous systemic psoriasis therapy
  - Type of psoriasis, psoriatic arthritis, years since psoriasis diagnosis, percentage of body surface area with psoriasis lesions, PASI score, PGA score, and DLQI score at treatment start
- Description of treatment course:
  - Number of patients and cumulative person-time of follow-up accrued in each study cohort
  - Number and percentage of patients who discontinued treatment in each cohort
  - Description of reasons for discontinuation

  - Dose of Skilarence at treatment initiation and first maintenance dose, in three categories: above the recommended dose, below the recommended dose, and recommended dose, where available

- Analyses conducted for each primary study outcome:
  - Incidence rates for patients initiating Skilarence and for patients initiating conventional systemic therapies will be estimated overall and stratified by relevant factors measured at baseline (listed in the Variables section), at least by defined special patient populations (i.e., patients aged over 65 years; pregnant and lactating woman; patients with renal impairment, hepatic impairment, gastrointestinal disease, or preexisting infections and immunosuppressed patients) if the number of patients is sufficient.
  - IRR estimates comparing Skilarence and conventional systemic therapies will be calculated. Crude, stratified, and adjusted IRR estimates will be presented. Adjustment for relevant baseline characteristics will be performed through multivariable modelling, to the extent that is possible with the accrued number of patients.
  - Point estimates from pooled analysis of point estimates from the three registers: incidence rates, overall and stratified by selected factors, and IRRs adjusted for relevant factors.
- Depending on scientific interest and the distribution of the data, subsequent exploratory analyses may be performed
- Description of all “other” SAEs and all AEs in each cohort, by MedDRA SOC:
  - Number of each type of event reported
  - Number and percentage of patients with each type of event
  - Cumulative number of patients with each type of event per 100 patient-years

Milestones[*]:

Start of data collection, Q1 2019

End of data collection, Q1 2027

Study progress report(s), annually, starting in Q2 2019

Final report of study results, within 1 year of availability of final data analytical set

[*] Contracts between the marketing authorisation holder and research organisation(s) and approvals by data protection, data custodian, ethics, and scientific review bodies are pending. Timelines may be impacted by approvals of these bodies, duration of contract reviews, and availability of data and staff at research institutions once contracts and approvals are finalised.

5 Amendments and Updates

Version Number	Date	Section of Study Protocol	Amendment or Update	Reason
1.2	14 Jun 2018	Title page, signature pages	Updated	To update date, version, and author information
1.2	14 Jun 2018	Section 3, Responsible Parties	Updated	To include researchers from collaborating organisations
1.2	14 Jun 2018	Section 4, Abstract	Updated	To update changes throughout protocol
1.2	14 Jun 2018	Section 6, Milestones and Timeline	Updated	To adjust timelines according to the anticipated date of protocol endorsement
1.2	14 Jun 2018	Section 9.1, Study Design	Updated	To update study overview graph with updated timelines
1.2	14 Jun 2018	Section 9.2, Setting; Section 9.3.2, Exposure Assessment	Updated	To provide additional details on the composition of comparator cohorts and clarification on the study period and follow-up in each register (response to PRAC assessment, 22 Mar 2018)
1.2	14 Jun 2018	Section 9.3.1, Safety Study Endpoints; Annex 3	Updated	To include operational terms (MedDRA) to define primary safety outcomes (request of PRAC, 22 Mar 2018)
1.2	14 Jun 2018	Section 9.3.2, Exposure Assessment	Updated	To include detailed information on reasons of treatment discontinuation and time at risk (response to PRAC assessment, 22 Mar 2018)
1.2	14 Jun 2018	Section 9.3.3, Other Variables	Updated	To include prior treatment of psoriasis and laboratory values variables (response to PRAC assessment, 22 Mar 2018)

1.2	14 Jun 2018	Section 9.7, Data Analysis	Updated	To include clarification on how other FAE group, informative censoring and confounding by indication will be handled (response to PRAC assessment, 22 Mar 2018) BADBIR confirmed that the registry can provide standard analysis for the annual updates and for the final report. Added Annex 4 with example of periodic report.
1.2	14 Jun 2018	Section 9.8, Quality Control	Updated	To provide additional details on the specific activities undertaken by each register to ensure reliability and validity of data (response to PRAC assessment, 22 Mar 2018)
1.2	14 Jun 2018	Section 9.9, Limitations	Updated	To expand discussion and include informative censoring, follow-up of renal and hepatic impairment, completeness of data and confounding by indication (response to PRAC assessment, 22 Mar 2018)
1.1	19 Dec 2017	Section 4, Abstract	Updated with changes throughout protocol	Feedback provided by participating registers
1.1	19 Dec 2017	Section 6, Milestones and Timeline	Update	Timelines adjusted to the expected date of protocol approval
1.1	19 Dec 2017	Section 9, Research Methods	Amendment	Feedback provided by participating registers, and adjust to specifics of registers' methods
1.1	19 Dec 2017	Section 11, Management and Reporting of Adverse Events/Adverse Reactions	Update	Feedback provided by participating registers

FAE = fumaric acid ester; MedDRA = Medical Dictionary for Regulatory Activities; PRAC = Pharmacovigilance Risk Assessment Committee.

6 Milestones and Timeline

The study timelines will be based on the anticipated timing of launch and reimbursement approval of Skilarence in the selected countries. Study timelines may be altered as a function of changes in the approval dates.

Contacts with the lead investigators of the selected registers have been established.

Study milestones are listed in Table 1.

Table 1. List of Study Milestones and Planned Dates

Milestone	Date
EMA protocol endorsement	Q4 2018[a]
Registration in the EU PAS Register	Q4 2018, after regulatory endorsement of the protocol and prior to start of data collection[a]
Skilarence launch	
Germany	01 Oct 2017
Spain	Q3 2018
United Kingdom	15 Sep 2017
Start of data collection [b]	Q1 2019
End of data collection [c]	Q1 2027
Study progress report(s)	Annually, starting in Q2 2019
Interim report	None planned
Final report of study results	Within 1 year of availability of final analytical data set

Q1 = first quarter; Q2 = second quarter; Q3 = third quarter; Q4 = fourth quarter; EMA = European Medicines Agency; EU = European Union; PAS = post-authorisation studies; PRAC = Pharmacovigilance Risk Assessment Committee.

Note: Contracts between the marketing authorisation holder and research organisation(s) and approvals by data protection, data custodian, ethics, and scientific review bodies are pending. Timelines may be affected by approvals of these bodies, duration of contract reviews, and availability of data and staff at research institutions once contracts and approvals are finalised.

[a] The date of protocol approval by EMA/PRAC and the availability of the product will drive the timing of subsequent study milestones.

[b] Date from which data extraction starts for study patients enrolled in the register after product is available in each country and the protocol is endorsed. For example, with a launch date of 15 September 2017 in the UK and 01 October 2017 in Germany and protocol endorsement in Q4 2018, data collection (i.e., extraction) in BADBIR and PsoBest register would start in Q1 2019, assuming 6 monthly fixed data cut-off dates for data analysis. The routine schedule of data extraction and reporting periods established by the registers vary: PsoBest and BADBIR data cut-offs are 30 June and 31 December; BIOBADADERM data cut-off by the end of November.

[c] Date from which the final analytical data set is available.

7 Rationale and Background

Psoriasis is a chronic inflammatory skin disorder that results from complex interactions between genes, the immune system, and environmental factors, although the exact cause remains unclear (Nestle et al., 2009; Schon and Boehncke, 2005). The disease can have a substantial impact on the quality of life of patients caused by both physical and psychological symptoms (Augustin et al., 2016; Krueger et al., 2001). Psoriasis also has an economic impact on patients and the health care system (Colombo et al., 2008; Schaefer et al., 2015). In Western countries, the estimated prevalence of psoriasis ranges from 2% to 4%, with a higher prevalence in northern countries, and it varies according to age (Parisi et al., 2013; Schafer, 2006). The relative frequency of moderate to severe psoriasis, which requires systemic treatment, has been reported to represent about 25% of all cases (Feldman et al., 2014).

Skilarence is a gastroresistant tablet formulation of dimethyl fumarate (DMF) developed by Almirall S.A. (Almirall) for the treatment of moderate to severe chronic plaque psoriasis in adult patients in need of systemic therapy. Oral fumaric acid esters (FAE), including DMF, belong to the therapeutic class of immunomodulating agents that are effective in the treatment of psoriasis. In 2011 FAE were included as recommended first-line systemic agents for moderate to severe psoriasis in the European S3 guidelines for psoriasis (Nast et al., 2015). FAE, which contain DMF and salts of ethyl-hydrogen fumarate, were approved for the treatment of moderate to severe psoriasis in Germany in 1994 where it is used as a first-line systemic therapy. Outside of Germany there is limited off-label use of FAE (Harries et al., 2005; Sladden et al., 2006; Wain et al., 2010).

The safety profile of FAE is characterised by frequent reports of gastrointestinal adverse events (AEs) and flushing that may lead to treatment withdrawal (Atwan et al., 2015; Atwan et al., 2016). Leukopenia, lymphocytopenia, and eosinophilia are also commonly reported, but they are generally reversible with treatment discontinuation. Elevation of liver enzymes, serum creatinine, and proteinuria have also been observed with FAE treatment. There have been cases of progressive multifocal leukoencephalopathy (PML) reported, most of them occurring in patients with severe lymphopenia, and reports of Fanconi syndrome associated with FAE (Balak et al., 2016a; Balak et al., 2016b).

The Skilarence pivotal phase 3 study 1102 showed that the safety profile of DMF alone was comparable to that of Fumaderm® (FAE). The main side effects observed were gastrointestinal symptoms and flushing, and other AEs occurred with similar frequency. There is a lack of data on the long-term safety of the Skilarence formulation, as well as safety in populations not included in the clinical trials. In November 2015, Almirall submitted to the European Medicines Agency (EMA), via a centralised procedure, the Marketing Authorisation Application (MAA) for Skilarence for the treatment of moderate to severe psoriasis, including the Risk Management Plan for Skilarence. The Committee for Medicinal Products for Human Use (CHMP) requested data on the long-term safety of Skilarence in the post-marketing setting, with a focus on safety concerns of interest (serious infections, malignancies, and all types of renal injuries). Specifically, Almirall was asked to explore different options for collecting these data and to consider the use of one or more psoriasis-specific patient registers to conduct a post-authorisation safety study (PASS).

The present document describes the common protocol for conducting a European, multinational observational PASS using data collected from patients with psoriasis enrolled in established psoriasis-specific registers of patients treated with systemic therapies.

The study will evaluate populations covered in three registers of patients: one each in Germany and Spain and one covering patients in the United Kingdom (UK) and Republic of Ireland. The use of data collected in large observational registers of patients with psoriasis treated with systemic therapies is expected to provide an additional source of safety data, as well as information on the characteristics of users of Skilarence enrolled in the registers.

8 Research Question and Objectives

This study aims to evaluate the long-term safety of Skilarence used for the treatment of patients with moderate to severe psoriasis. The study seeks to evaluate whether the use of Skilarence is associated with an increased risk of serious infections (including serious opportunistic infections such as PML), malignancies, or renal impairment, as compared with conventional (non-biologic) systemic therapies (hereafter, “conventional systemic therapies”). In addition, the study aims to describe the use of Skilarence, in particular in patient subgroups for which there is missing information in the Risk Management Plan.

The specific primary objectives are the following:

- To evaluate the risk of serious infections—overall, serious opportunistic infections, and PML individually—in new users of Skilarence compared with new users of conventional systemic therapies
- To evaluate the risk of malignancies in new users of Skilarence compared with new users of conventional systemic therapies
- To evaluate the risk of all types of renal impairment events (including Fanconi syndrome) in new users of Skilarence compared with new users of conventional systemic therapies
- To describe the characteristics of patients with psoriasis who initiate treatment with Skilarence and of patients with psoriasis who initiate treatment with conventional systemic therapies

The secondary objectives are the following:

- To evaluate the incidence of all “other” serious AEs (SAEs) (other than those covered by the primary objectives), by MedDRA* System Organ Class (SOC)
- To evaluate the incidence of all AEs by MedDRA SOC
- To evaluate safety data for the following special populations of patients with psoriasis treated with Skilarence: patients aged over 65 years; pregnant and lactating woman; patients with renal impairment, hepatic impairment, gastrointestinal disease, or preexisting infections; and immunosuppressed patients

* MedDRA = Medical Dictionary for Regulatory Activities (http://www.meddra.org/).

9 Research Methods

9.1 Study Design

This is a long-term, non-interventional, observational PASS that will use a prospective cohort design and data primarily collected in established registers of patients with psoriasis treated with systemic therapies in European countries.

Data from the registers will be used to identify cohorts of patients with psoriasis who are new users of Skilarence or who initiate treatment with conventional systemic therapies. Conventional systemic therapies will include oral psoralen plus ultraviolet A radiation (PUVA), methotrexate, ciclosporin, FAEs, and oral retinoids (e.g., acitretin)—as included by each register. Patients will be characterised at baseline and followed from cohort entry through 31 December 2026 to determine the incidence of the safety concerns of interest. Follow-up of patients is expected to range from 2 months to 9 years, depending on the date of cohort entry.

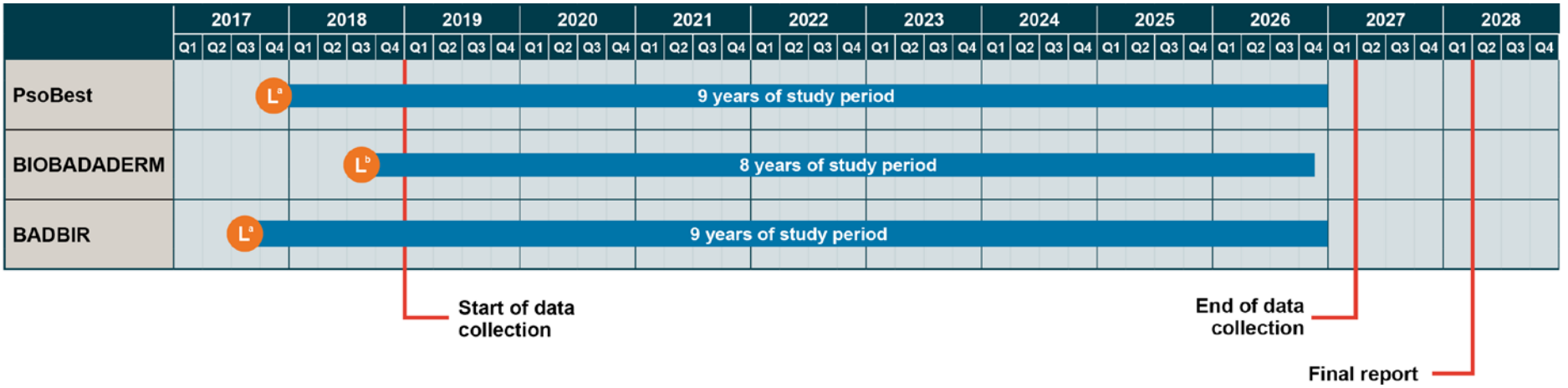
The psoriasis registers for systemic therapies were set up to monitor the effectiveness and long-term safety of biologic therapies and compare them to that of conventional systemic therapies in routine clinical practice. Typically, the registers target a number of patients on a new biologic therapy and recommend enrolling at least one patient starting treatment with any conventional systemic therapy for each patient on a biologic therapy who is enrolled. The registers are typically open to participation by medical specialists who enrol patients from all levels of care such as dermatology practices and hospital-based outpatient clinics.

The registers collect data on patient demographics; lifestyle factors; comorbidities and medications used to treat them; type of psoriasis; physician and patient assessments of the psoriasis; treatment of psoriasis; and any AE, including serious AE (SAE).

The study is proposed to be conducted in the following countries and patient registers:

- Germany—the German Register on the Treatment of Psoriasis With Biologics and Systemics (PsoBest)
- Spain—the Spanish Register of Systemic Therapy in Psoriasis (BIOBADADERM)
- UK and Republic of Ireland—the British Association of Dermatologists Biological Interventions Register (BADBIR)

Figure 1. Study Overview



BADBIR = British Association of Dermatologists Biological Interventions Register; BIOBADADERM = Spanish Register of Systemic Therapy in Psoriasis; PsoBest = German Register on the Treatment of Psoriasis with Biologics and Systemics.

[a] Skilarence launch date (L) and expected date of start of study period in PsoBest (01 October 2017) and BADBIR (15 September 2017).

[b] Preliminary estimated Skilarence launch date (L) and expected date of start of study period in BIOBADADERM is at the beginning of Q3 2018.

Note: The estimated start of data collection is Q1 2019, with first data extraction from PsoBest and BADBIR with cut-off date of 31 December 2018. Routine schedule of data extraction and reporting periods established by the registers vary: PsoBest and BADBIR data cut-offs are 30 June and 31 December; BIOBADADERM has an annual data cut-off at the end of November.

Note: Study progress reports will be scheduled annually, starting in Q2 2019.

9.2 Setting

9.2.1 Population

The source population will consist of patients with psoriasis who initiate treatment with a systemic therapy in regular clinical practice in selected European countries.

Patients will be eligible to enter in the study cohort if they meet the following criteria: are diagnosed with psoriasis, have initiated treatment with Skilarence or a conventional systemic therapy, and have given consent to be enrolled in the selected established registers for psoriasis between the date Skilarence became available in the selected country and the end of the study period.

Patients will be excluded if they are enrolled in a clinical trial, or do not qualify for or do not give consent for enrolment in the register. Specific inclusion/exclusion criteria of each selected register will need to be considered (Table 2).

Table 2. Inclusion and Exclusion Criteria for the Conventional Systemic Therapy Cohorts in Each Study Register

	PsoBest, Germany	BIOBADADERM, Spain	BADBIR, UK, and the Republic of Ireland
Inclusion criteria	▪ Patients aged ≥ 18 years, with plaque-type psoriasis or psoriatic arthritis ▪ Patient initiates a specific systemic therapy for the first time ▪ Patient has sufficient language skills (German) and is able to give written informed consent to participate	Patients with psoriasis initiating a conventional systemic therapy for the first time and having never received a biologic systemic therapy or newly approved systemic medications	Patients willing to give informed consent Diagnosis of moderate to severe psoriasis under the care of a dermatologist Patients initiating or switching conventional systemic therapy within the previous 6 months. If not switching therapy, patient must have PASI ≥ 10 and DLQ1 > 10 Never exposed to a biologic therapy or non-biologic small-molecule immunotherapy Willing to give informed consent for long-term follow-up and access to all medical records
Exclusion criteria	Lack of informed consent Patients participating in clinical trials at the day of admission to the register	Intention to move to a different geographic area in the next 3 months	Participation in blinded clinical trials Patients ever exposed to biological therapy

BADBIR = British Association of Dermatologists Biological Interventions Register; BIOBADADERM = Spanish Register of Systemic Therapy in Psoriasis; PsoBest = German Register on the Treatment of Psoriasis with Biologics and Systemics; UK = United Kingdom.

The study population will be grouped into two cohorts, as follows:

- Skilarence cohort: patients will qualify to enter in the Skilarence cohort if they initiate or switch to Skilarence treatment after the date Skilarence becomes available in the country and have given consent to participate in the register.
- Conventional systemic cohort: patients will qualify to enter in the conventional systemic cohort if they initiate treatment with a conventional systemic therapy after the date Skilarence becomes available in the country, have not received any newly approved systemic medication, and have given consent to participate in the register. Patients in the conventional systemic cohort can have received other systemic medication previously (not newly approved) before the study entry. This will constitute the comparator cohort and will take into account the specific treatments recorded at each register.
    - In PsoBest, the conventional systemic cohort will include patients treated with FAEs, methotrexate, ciclosporin, and acitretin (with the latter mainly in combination with PUVA). A subcohort including patients treated with FAEs will be considered for the final analyses at the end of the study.
    - In BIOBADADERM, the conventional systemic cohort consists of patients initiating or switching conventional therapy with PUVA, ciclosporin, methotrexate, or acitretin. However, per the register's standard approach in the annual analyses, the conventional systemic cohort will consist of patients treated with methotrexate because this has a well-established safety profile and is the most frequent treatment among the conventional systemic treatments. This allows a homogeneous group for comparison. Other conventional systemic therapies can be included in the final analyses.
    - In BADBIR, the conventional systemic cohort consists of patients initiating or switching conventional therapy with PUVA, ciclosporin, methotrexate, FAEs, acitretin, or hydroxycarbamide. If not switching therapy, patients must have the severity criteria for biologic therapy. The BADBIR standard Manchester Template reports will include all of the comparator cohort in BADBIR (i.e., including patients enrolled prior to Skilarence becomes available).

9.2.2 Study Period

In each register, the study period is defined as the time from the date when Skilarence became available in the corresponding country through 31 December 2026, allowing at least 8 years of patient enrolment in the last data source incorporated into the study, and follow-up expected to range from 2 months to 9 years (Table 3). Annual reports will be produced to describe the number of new users of Skilarence enrolled in each database.

Table 3. Estimated Study Period in Each Study Register

	PsoBest, Germany	BIOBADADERM, Spain	BADBIR, UK, and the Republic of Ireland
Skilarence launch in country[a]	01 Oct 2017	Q3 2018	15 Sept 2017
Enrollment period	01 Oct 2017 to 30 Sept 2026	Q3 2018 to 30 Sept 2026	15 Sept 2017 to 30 Sept 2026
End of study period (based on Skilarence launch date in each country and an 8-year enrolment period in the last data source included in study)	31 Dec 2026	Nov 2026	31 Dec 2026

BADBIR = British Association of Dermatologists Biological Interventions Register; BIOBADADERM = Spanish Register of Systemic Therapy in Psoriasis; PsoBest = German Register on the Treatment of Psoriasis with Biologics and Systemics; Q3 = third quarter; UK = United Kingdom.

[a] Provided by Almirall.

9.2.3 Follow-up

Date of cohort entry will be the date of the first treatment with one of the cohort-defining medications—Skilarence or conventional systemic therapy—after other inclusion criteria have been met.

For the annual analyses, as per the registers standard periodic analyses and per the Manchester template report (see Section 9.3.2.1, Time at Risk), the date of end of follow-up will be defined as the earliest of the following events: exiting the register, death, end of study period or any of the following censoring events:

- Initiation of treatment with biologic agent
- Loss to follow-up as defined in the register
- Enrolment in a clinical trial

For the final study analyses of each separate primary safety outcome of interest in the study (i.e., any serious infection, serious opportunistic infection, PML, any malignancy, and renal impairment), the date of end of follow-up will be defined as the earliest of the following events: first occurrence of the study outcome of interest, exiting the register, death, end of study period, or any of the following censoring events:

- Initiation of treatment with biologic agent
- Loss to follow-up as defined in the register
- Enrolment in a clinical trial

The censoring of the follow-up due to the occurrence of one of the primary safety outcomes of interest does not represent the end of the follow-up for other safety outcomes of interest.

The study will take into consideration the specific procedures established by each register to handle data on patients who enter clinical trials while enrolled in the register.

9.3 Variables

Data collected by the registers will be used for ascertainment of variables, which will include patient demographics, psoriasis diagnosis and severity of disease, safety study endpoints, treatment exposure, and other variables, as available in each register.

9.3.1 Safety Study Endpoints

The following primary endpoints are of interest for the safety study:

- All serious infections: all SAEs of the MedDRA SOC infections and infestations
- Serious opportunistic infections (including PML): all SAEs with selected MedDRA terms specific to opportunistic infections that can be considered to be serious
- PML: All AEs with selected MedDRA terms specific to PML
- All malignancies: all AEs of the MedDRA SOC neoplasms benign, malignant, and unspecified (including cysts and polyps)
- All renal impairments, including Fanconi syndrome: all AEs of the MedDRA SOC renal and urinary disorders

The following secondary endpoints are of interest:

- All “other” SAEs, listed by MedDRA SOC
- In databases where this information is available, all AEs, listed by MedDRA SOC

The preliminary list of target MedDRA terms that will be used to identify the primary safety outcomes of interest is included in Appendix 3.

An AE is any untoward medical occurrence in a patient administered a medicinal product. An AE does not necessarily have a causal relationship with the medicinal product received. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the product or requires stopping the treatment or unplanned medical care is also considered an AE.

An adverse reaction is an AE which has a causal relationship with the product, that is, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility.

An SAE/reaction is an AE that, at any dose, meets any of the following conditions, disregarding causal relationship:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is an important medical event

Life-threatening means that the patient was at risk of death at any time point of the study. It is not an event that hypothetically may have resulted in death if the event had been more pronounced.

Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalisation may be considered an SAE when, based upon appropriate medical judgement, they may jeopardise the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed above.

Pregnancies of a female patient or of a female partner of a male patient are considered SAEs, irrespective of any occurrences of other (adverse) events.

9.3.2 Exposure Assessment

The main exposure of interest is treatment with Skilarence.

The comparator will be conventional systemic therapies for psoriasis—oral psoralen plus ultraviolet A radiation (PUVA), methotrexate, ciclosporin, FAEs, and oral retinoids (e.g., acitretin)—as included by each register.

- Other FAEs will be included in a third cohort in PsoBest (Germany) in the final analyses.
- In BIOBADADERM, only patients taking methotrexate will be included in the comparator group. However, other conventional systemic therapies will be included in the final analyses.
- In BADBIR (UK), the number of patients treated with other FAEs is expected to be minimal or none since Skilarence was marketed and will be included in the conventional systemic cohort.

The following characteristics of exposure will be captured:

- Where information is available, dose of Skilarence at treatment start and first maintenance dose, in three categories: above the recommended dose, below the recommended dose, and recommended dose
- Duration of treatment
- Discontinuation of treatment and reason(s) as collected in each register to identify informative censoring. The reasons for treatment discontinuation collected in each register are as follows:
    - In PsoBest, contraindication, recovery, side effects, and others (classified from text directly reported by physicians)
    - In BIOBADADERM, lack of efficacy, inefficacy, AEs, pregnancy, loss to follow-up, remission, and others
    - In BADBIR, lack of efficacy, remission, inefficacy and AEs, patient noncompliance, titration, financial consideration, and patient choice

9.3.2.1 Time at Risk

In the cohort study, incidence rates for any of the study endpoints will be calculated during current use of Skilarence and current use of other conventional systemic therapies in each respective cohort. In the participating registers, an event will be assigned to a patient of a treatment cohort if the date of the event is at the day of start of treatment, in the period between start and stop of the treatment, or within 90 days after the end of treatment, regardless of comedication.

Events observed for combined or overlapping treatments (as defined in the "90-day rule" risk window recommended by the European Network of Psoriasis Registries (Psonet) based on the "Manchester Template" elaborated by the European Rheumatology Biologic Registers) will be assigned to each treatment, except for malignancies and pregnancy, delivery, and perinatal events. For any therapy, the risk window for malignancies and deaths includes all prospective person-time documented in the register for a specific therapy and extends until the date of the event, the date of the last observation, or the end of the actual report period, whichever comes first. Pregnancy, delivery, and perinatal events will be assigned to a treatment cohort if the date of the event is at the day of start of treatment, in the period between start and stop of the treatment, or within 1 year after the end of treatment, regardless of comedication.

For the annual analyses, for all AEs, time at risk, per standard practice of the registers, will be all person-time documented in the register as exposed to a drug since it was started to the end of reporting period, loss to follow-up, or death. This will be the same for all AEs.

For the final study analysis, registers will deviate from the standard analyses, and for each primary outcome of interest, time at risk will be all person-time of exposure to a drug since it was started to the date of the first occurrence of the outcome of interest.

9.3.3 Other Variables

The characterisation of study cohorts will be based on the data collected or derived from data collected at cohort entry in the psoriasis registers (Table 4):

- Demographics: age, sex
- Body mass index, smoking status, and alcohol use, as available in each register
- Specific baseline comorbidities, including but not limited to renal, hepatic, and gastrointestinal diseases; preexisting infections; and immunosuppressive conditions at treatment start
- Comedications at baseline, including but not limited to immunosuppressants and nephrotoxic and hepatotoxic medications, where available.
- Previous systemic psoriasis therapy, where available
- Laboratory tests results (creatinine, transaminase [ALT]) may be available in BADBIR at baseline and during the follow-up for 3 years as reported by physicians.
- Type of psoriasis, psoriatic arthritis, years since psoriasis diagnosis, percentage of body surface area with psoriasis lesions and PASI score, PGA score, and DLQI score at treatment start, as available in each register

Table 4. Data Collected by Psoriasis Registers

	PsoBest	BIOBADADERM	BADBIR
Age, sex	Yes	Yes	Yes
Body mass index	Yes	Yes (at entry)	Yes
Smoking status	Yes (as comorbidity)	Yes (at entry)	Yes
Alcohol	Yes (as comorbidity)	Yes (at entry)	Yes
Baseline comorbidities	Cardiovascular, metabolic, infectious, liver, gastrointestinal, renal, pulmonary, rheumatic and immunological, psychiatric and addiction, neurological, and dermatological-allergological	Cardiovascular, hypertension, diabetes mellitus, dyslipidaemia, chronic obstructive pulmonary disease, liver, kidney, malignancy, hepatitis	Hypertension, cardiovascular disease, diabetes mellitus, autoimmune disorders, thrombosis, liver disease, kidney disease, multiple sclerosis, and non–skin cancer, among others
Comedications	Other psoriasis medications. Other medications are captured if a baseline comorbidity is treated.	Other psoriasis medications; other medications at the time of an AE	All patients' current therapy for any indication
Laboratory test values	No	No	Yes
Type of psoriasis, psoriatic arthritis, years since psoriasis diagnosis	Yes	Yes	Yes
Severity of psoriasis	Yes	Yes	Yes

BADBIR = British Association of Dermatologists Biological Interventions Register; BIOBADADERM = Spanish Register of Systemic Therapy in Psoriasis; PsoBest = German Register on the Treatment of Psoriasis with Biologics and Systemics.

9.4 Data Sources

Based on knowledge of the countries where a register of patients with psoriasis treated with systemic therapies is available, the availability of a network of experienced dermatologists, and the sales forecast for Skilarence, the proposed candidate countries for the conduct of the study are Germany, Spain, the UK, and the Republic of Ireland. Changes in the anticipated availability of Skilarence to be prescribed in these countries may lead to changes in the proposed targeted countries.

The following European patient registers are proposed as data sources for performing a PASS for Skilarence:

- PsoBest (Germany)
- BIOBADADERM (Spain)
- BADBIR (UK and Republic of Ireland)

9.4.1 PsoBest

PsoBest (German Register on the Treatment of Psoriasis With Biologics and Systemics) is a register of patients with psoriasis and psoriatic arthritis established in December 2007 to evaluate the long-term outcomes in adult patients treated with biologic or conventional systemic therapies in Germany. The register is housed at the German Centre for Health Services Research in Dermatology (Reich et al., 2015). The register enrols adult patients with moderate to severe psoriasis who initiate a treatment with biologics (adalimumab, etanercept, infliximab, ustekinumab and golimumab) or conventional systemic therapy (fumaric acid esters [FAE], methotrexate, ciclosporin A, retinoids, leflunomide, systemic psoralen plus ultraviolet A radiation [PUVA]). Each patient is followed for a period of 10 years, independently of the treatment applied. Follow-up visits in the dermatology office are conducted every 3 months in the first 6 months and every 6 months afterwards. In addition, 3 months after the physician visits, the patients are contacted by mail to collect further information on treatment status and patient-reported outcomes. The estimated proportion of the German population sampled by the register was 10% with 530 hospitals and private practices, capturing an estimated 0.25% of all psoriatic patients receiving biologics (Ormerod et al., 2012). At present, 691 dermatology practices and 64 hospital outpatient clinics actively participate in PsoBest (Augustin et al., 2016). PsoBest has data on more than 4,000 patients, with about 270 centres providing 90% of data. The inclusion/exclusion criteria are described in Table 2 in Section 9.2.1.

Information on any AEs and SAEs is collected in PsoBest.

PsoBest is part of the Psonet, a network of independent European registers of patients suffering from psoriasis or psoriatic arthritis and being treated by systemic agents (Psonet, 2007). As part of Psonet, PsoBest follows a common protocol. The assessment of safety in Psonet has been adapted to meet the procedures of the German Register on Biologics and Rheumatoid Arthritis (Zink et al., 2001) and European recommendations (EMA, 2017b).

9.4.2 BIOBADADERM

BIOBADADERM is a prospective cohort of patients with moderate to severe psoriasis receiving systemic therapy (Rivera et al., 2011). Patients from 14 Spanish hospitals have been enrolled into the cohort since 2008. Patients are included when they are first prescribed any specific conventional or new systemic treatment (biologics and non-biologics), and they are followed up continuously thereafter (initial follow-up was planned for 5 years but it was extended). Participating centres are requested to include all patients starting new systemic treatments for the first time who meet the inclusion criteria. A control receiving classic systemic therapy (e.g., acitretin, methotrexate, ciclosporin) who has not previously been treated with a new systemic treatment is enrolled for each patient added to the new systemic treatments group (Table 2 in Section 9.2.1). These criteria should produce an initial population in which 50% of patients are starting new systemic therapy and 50% are starting classic systemic therapy.

Data collection includes demographic data, diagnoses, and comorbidities. Each new patient is registered with the corresponding drug start and, if and when applicable, discontinuation dates and reasons for discontinuation. The register records all AEs reported, with date of occurrence, description using MedDRA coding terms, concomitant

therapies, severity, and outcome. Patients are contacted at least once a year, although most patients are seen at the centres more frequently as part of their regular care. Patient diaries with questions relating to SAEs are used to improve outcome reporting. Data monitoring includes online continuous monitoring and yearly on-site monitoring of a random sample of patients, which focuses on drug exposures and SAEs, and through reviewing patient records.

All AEs that are serious (according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use E2A Guideline 12) or lead to a change in therapy or to unexpected medical attention are included in the register. According to most recent report (FAEDV, 2017), 2,736 patients have been enrolled in BIOBADADERM from October 2008 through November 2017.

9.4.3 BADBIR

The BADBIR is a large prospective observational patient register including three cohorts of patients with a diagnosis of psoriasis: a cohort consisting of patients treated with biologic treatments, a cohort of patients on small-molecule immunomodulatory therapy, and a control cohort with similar disease characteristics but treated with conventional systemic treatments (BADBIR, 2017). Each patient is followed for a period of 5 years or to the end of the study (currently 2028), whichever occurs last. Follow-up visits are conducted every 6 months during the first 3 years and then annually for subsequent years. The inclusion/exclusion criteria are described in Table 2 in Section 9.2.1.

As in PsoBest, information on any AE is collected in the BADBIR. All AEs are collected and reported in each follow-up; all AEs are reviewed and coded by pharmacovigilance experts using MedDRA, and SAEs are reported to the corresponding product manufacturers within 24 hours of receipt of the event report by the register (BADBIR, 2016; Burden et al., 2012).

The register coverage includes the UK and Republic of Ireland, and participation is open to all dermatologists. Guidelines in the UK recommend the registration of patients with psoriasis receiving biologics in the BADBIR (Smith et al., 2009). The register took the British Society for Rheumatology Biologics Register as the model for the study design, funding structure, and pharmacovigilance obligations (Watson et al., 2005). Since 2012, the National Institute for Health and Care Excellence's recommendation to specialists is to offer patients with psoriasis treated with systemic therapies (biological and non-biological) the opportunity to participate in long-term registers such as the BADBIR (National Institute for Health and Care Excellence, 2012). This has been pointed out as a contributor to the increase of the enrolment rates and number of participant sites in recent years. As of June 2016 there were 12,265 patients registered in the BADBIR and 153 participant centres across the UK and Ireland (Biologic Interventions Register, 2016).

9.5 Study Size

The study size will be driven by the uptake of Skilarence after it becomes available to prescribe following product launch and, where applicable, reimbursement approval in each of the selected countries.

Germany and the UK are the two countries with the highest forecasted sales, followed by Spain, Italy, and Sweden. The defined daily dose (DDD) for Skilarence is 360 mg/day,

and the dose needs to be adjusted individually to each patient. This complicates estimating the number of patients treated in each country from sales data.

There are no specific a priori hypotheses to be evaluated, but it is expected that patients in the Skilarence group will have similar incidence rates of serious infections, serious opportunistic infections, PML, malignancies, and all types of renal impairment as patients in the other conventional systemic therapies group.

The number of patient-years of Skilarence exposure required to detect an increase in risk of the safety events of interest in Skilarence patients compared with patients on other conventional systemic therapies have been calculated (Table 5). The calculations, using the variance stabilising transformation test statistic (Gu et al., 2008), assumed person-time ratios (Skilarence to other conventional systemic therapies) of 1:1 and 1:2 and a power of 80% for a two-sided significance of alpha = 0.05. The study size calculations have considered the incidence rates of the safety events of interest in a cohort of users of FAE and other conventional (non-biologic) systemic therapies reported previously (IVDP, 2015), population-based incidence rates of kidney cancer (IARC, 2012), and an estimate of incidence of PML in patients with rheumatic diseases (Bharat et al., 2012).

Assuming an incidence rate of serious infections of 0.77 per 100 person-years and a similar estimated incidence rate for all types of renal impairment events, 3,316 person-years of risk accumulated in the Skilarence cohort are required to detect an incidence rate ratio (IRR) of 2 for the comparison of Skilarence with other conventional systemic therapies in the scenario of equal follow-up time in each group (1:1 person-time ratio). In the scenario with a person-time ratio of 1:2 (twice as much person-time at risk for the other conventional systemic therapies cohort), 2,401 person-years of risk in the Skilarence cohort are required to detect the same IRR of 2.

Assuming an incidence rate of PML of 0.2 per 100,000 patients (Bharat et al., 2012), 12,845,588 person-years of risk accumulated in the Skilarence cohort are required to detect an IRR of 2 for the comparison of Skilarence with other conventional systemic therapies in the scenario of equal follow-up time in each group (1:1 person-time ratio). In the scenario with a person-time ratio of 1:2 (twice as much person-time at risk for the other conventional systemic therapies cohort), 9,299,518 person-years of risk in the Skilarence cohort are required to detect the same IRR of 2.

Assuming an incidence rate of malignancies of 1.05 per 100 person-years, 2,443 person-years of risk accumulated in the Skilarence cohort are required to detect an IRR of 2 for the comparison of Skilarence with other conventional systemic therapies in the scenario of equal follow-up time in each group (1:1 person-time ratio). In the scenario with a person-time ratio of 1:2, 1,769 person-years of risk in the Skilarence cohort are required to detect the same IRR of 2.

For specific types of malignancies, such as kidney cancer, assuming the same incidence rate of 13.8 per 100,000 persons per year as occurs in the general population of Spain (IARC, 2012), 186,168 person-years of risk accumulated in the Skilarence cohort are required to detect an IRR of 2 for the comparison of Skilarence with other conventional systemic therapies in the scenario of equal follow-up time in each group (1:1 person-time ratio). In the scenario with a person-time ratio of 1:2, 134,776 person-years of risk in the Skilarence cohort are required to detect the same IRR of 2.

Table 5. Number of Skilarence-Exposed Person-Years Needed to Detect Various IRRs Using a Two-Sided Test for the Ratio of Two Poisson Rates (Alpha = 0.05; Power = 0.80)

	Background Incidence Rate[a]	Skilarence-to-Comparator Ratio = 1:1						Skilarence-to-Comparator Ratio = 1:2					
		IRR, 1.5	IRR, 2.0	IRR, 2.5	IRR, 3.0	IRR, 3.5	IRR, 4.0	IRR, 1.5	IRR, 2.0	IRR, 2.5	IRR, 3.0	IRR, 3.5	IRR, 4.0
Infections													
AEs other systemic	8.41[b]	986	305	162	106	77	60	724	221	116	75	54	42
AEs fumaric acid esters	4.48[b]	1,850	573	304	198	144	112	1,359	415	217	141	102	79
SAEs other systemic	0.82[b]	10,080	3,123	1,654	1,080	787	613	7,405	2,261	1,184	767	555	430
SAEs fumaric acid esters	0.77[b]	10,704	3,316	1,757	1,147	835	650	7,863	2,401	1,258	814	589	456
SAEs non-methotrexate/ non-biologic	1.05[c]	7,887	2,443	1,294	845	615	479	5,794	1,769	927	600	434	336
SAEs methotrexate/ non-biologic	1.28[c]	6,479	2,008	1,064	695	506	394	4,760	1,454	762	493	357	277
Malignancies													
Other systemic	1.20[d]	6,930	2,147	1,137	742	541	421	5,091	1,554	814	527	381	295
Fumaric acid esters	1.05[d]	7,887	2,443	1,294	845	615	479	5,794	1,769	927	600	434	336
Non-biologics	0.81[e]	10,238	3,172	1,680	1,097	799	622	7,521	2,296	1,203	779	563	436
Kidney cancer[f]													
Germany	0.0227	365,324	113,177	59,951	39,136	28,508	22,200	268,385	81,934	42,926	27,784	20,102	15,568
Spain	0.0138	600,931	186,168	98,615	64,377	46,894	36,517	441,474	134,776	70,611	45,703	33,067	25,608
United Kingdom	0.0155	535,023	165,750	87,799	57,316	41,751	32,512	393,054	119,994	62,866	40,691	29,440	22,799

	Background Incidence Rate[a]	Skilarence-to-Comparator Ratio = 1:1						Skilarence-to-Comparator Ratio = 1:2					
		IRR, 1.5	IRR, 2.0	IRR, 2.5	IRR, 3.0	IRR, 3.5	IRR, 4.0	IRR, 1.5	IRR, 2.0	IRR, 2.5	IRR, 3.0	IRR, 3.5	IRR, 4.0
Renal and urinary disorders													
AEs other systemic	0.93[b]	8,871	2,748	1,456	950	692	539	6,517	1,989	1,042	675	488	378
AE fumaric acid esters	0.77[b]	10,704	3,316	1,757	1,147	835	650	7,863	2,401	1,258	814	589	456
SAEs other systemic	0.07[b]	10,883	34,351	18,196	11,879	8,653	6,738	81,460	24,868	13,029	8,433	6,101	4,725
SAEs fumaric acid esters	0.11[b]	74,926	23,212	12,296	8,027	5,847	4,553	55,044	16,804	8,804	5,698	4,123	3,193
Progressive multifocal leukoencephalopa-thy	0.0002	41,464,271	12,845,588	6,804,428	4,441,986	3,235,700	2,519,650	30,461,686	9,299,518	4,872,144	3,153,524	2,281,591	1,766,950

AEs = adverse events; IRR = incidence rate ratio; SAEs = serious adverse events; UK = United Kingdom.

Note: Calculations were performed using the variance stabilising transformation test statistic as described in Gu et al. (2008).

Note: IRR values denote the incidence rate of Skilarence exposure relative to the incidence rate of comparator exposure.

[a] Incidence rate per 100 person-years = number of events / total person-year * 100.

[b] Source: IVDP (2015).

[c] Source: Kalb et al. (2015).

[d] Incidence rate of malignancies including skin cancer (IVDP, 2015).

[e] Incidence rate of malignancies excluding non-melanoma skin cancers (Gottlieb et al., 2014).

[f] Source: IARC (2012). Data from general population-based cancer registers of the three countries were used to obtain a refence incidence rate of a rare malignancy to illustrate the person-time required to detect various IRRs. Similar data were not available from the study registers.

Enrolment figures from the targeted registers are shown in Table 6 through Table 8.

Table 6 presents the annual enrolment in PsoBest by individual systemic therapies each year for 2011-2015 and cumulative for the period 2007-2010. The total number of patients treated with FAEs enrolled in PsoBest since the register started through the end of 2015 is 1,409 patients, which represents 38.3% of the total number of patients enrolled in the register.

Table 6. The German Register on the Treatment of Psoriasis With Biologics and Systemics, PsoBest: Enrolment by Treatment and Year

Inclusion Medication	Total		Number of Inclusions Per Year					
	Frequency	Percentage	2007-2010[a]	2011	2012	2013	2014	2015
Fumaric acid esters	1,409	38.3	515	220	216	196	166	96
Methotrexate	877	23.8	279	116	152	120	131	79
Ciclosporin	214	5.8	83	32	33	25	30	11
Retinoids	58	1.6	18	11	5	11	7	6
Systemic PUVA	3	0.1	2	0	0	0	0	1
Anti–TNF-alpha	827	22.5	488	102	66	73	66	32
Adalimumab	446	12.1	214	62	44	59	43	24
Etanercept	242	6.6	166	23	17	12	18	6
Efalizumab	32	0.9	32	0	0	0	0	0
Infliximab	84	2.3	56	15	4	2	5	2
Golimumab	23	0.6	20	2	1	0	0	0
Anti-interleukin	294	8.0	90	37	38	37	40	52
Ustekinumab	270	7.3	90	37	38	37	40	28
Secukinumab	24	0.7	0	0	0	0	0	24
Total	3,682	100.0	1475	518	510	462	440	277

PUVA = psoralen and ultraviolet A; TNF = tumour necrosis factor.

[a] Total enrolment for the period from 2007 through 2010.

Source: Information received by Almirall from the PsoBest register owner (14 February 2017).

The cumulative enrolment in BIOBADADERM at the end of 2015, 2016, and 2017 is summarised in Table 7; there are no patients treated with FAEs enrolled in this register.

Table 7. BIOBADADERM—Spanish Register of Systemic Therapy in Psoriasis: Cumulative Enrolment Status

Medication	2015 Report (1 October 2008 to 10 November 2015)[a]	2016 Report (1 October 2008 to 21 November 2016)[a]	2017 Report (1 October 2008 to 6 November 2017)[a]
Etanercept	635	675	718
Adalimumab	683	725	765
Ustekinumab	560	649	736
Infliximab	184	188	188
Efalizumab	108	112	111
Secukinumab	—	101	204
Certolizumab	—	—	3
Apremilast	—	22	87
Infliximab biosimilar	—	3	17
Tildrakizumab	—	2	—
Ixekizumab	—	2	37
Etanercept biosimilar	—	1	9
Adalimumab biosimilar	—	—	1
Acitretin	467	536	611
Ciclosporin	472	510	596
Methotrexate	880	1,051	1,324
Total number of patients	2,261	2,456	2,736

Note: The total number of patients is larger than the sum of the number of patients for each individual medication because some patients received more than one medication during the period.

[a] Period from the date of start of BIOBADADERM to the date of data extraction.

Source: FAEDV (2015); FAEDV (2016); (FAEDV, 2017).

The cumulative numbers of participants recruited in the biologic and the conventional systemic therapy cohorts in the BADBIR register are presented in Table 8. The biologic cohort includes patients who initiate treatment with one biologic agent or biosimilar including adalimumab, secukinumab, etanercept, infliximab, ustekinumab, ixekizumab, and other. The cohort of conventional systemic therapy includes patients initiating or switching to conventional therapy with PUVA, ciclosporin, methotrexate, FAEs, acitretin, or hydroxycarbamide. As of August 2014, 7.6% of patients registered with BADBIR in the conventional systemic therapy cohort received FAEs, according to published data (Iskandar et al., 2015); currently, 8% of the conventional systemic cohort received FAEs at the time of registration, as reported by BADBIR in response to an Almirall query of 07 March 2017 (data on file).

Table 8. The British Association of Dermatologists Biological Interventions Register, BADBIR: Annual Cumulative Recruitment Status

Year of Report	Biologic Cohort	Conventional Systemic Therapy Cohort
2009	392	61
2010	854	207
2011	1,829	682
2012	2,834	1,347
2013	4,385	2,603
2014	5,394	3,181
2015	6,544	3,733
2016	7,960	4,352

Source: BADBIR Annual Progress Reports to Main Research Ethics Committee. Available at http://www.badbir.org/RandD/SiteFileDocuments/. Accessed 22 February 2017.

We estimated the potential accrual of person-time of exposure to Skilarence in the registers for a study period of 8 years using several assumptions related to the estimated population coverage by the register, prevalence of psoriasis and proportion of moderate to severe psoriasis, potential use of FAE and Skilarence, and dropout rate (Table 9). Several scenarios that varied in the magnitude of the assumptions, some of them difficult to anticipate, were considered, and the potential accrual data presented in Table 9 are approximate estimates with many uncertainties.

Table 9. Estimated Accrual of Patient-years for an 8-Year Study Period

	PsoBest, Germany	BIOBADADERM, Spain	BADBIR, UK, and the Republic of Ireland
Population of target country (millions)	80.62[a]	46.42[a]	65.14[a]
Population covered by register (%)	10[b]	< 10[b] (assumed 5)	50[b]
Prevalence of psoriasis (%)	2.5[c]	1.4[c]	1.9[c]
Proportion of patients with moderate to severe psoriasis	25[d]	25[d]	25[d]
Proportion of mod-severe psoriasis receiving FAEs	38.7[e]	3.0[f]	3.0[f]
Approximate percentage of eligible Skilarence users to enrol in study (%)	2	30	2
Potential number of patients to be enrolled in study each year	395	75[g]	91
Proportion of annual eligible patients actually enrolled in each year	[h]	[i]	[j]
Register dropout rate per year (%)	10	10	10
Total person-years after 8 years of follow-up	**3,219**	**1,932**	**1,155**

BADBIR = British Association of Dermatologists Biological Interventions Register; BIOBADADERM = Spanish Register of Systemic Therapy in Psoriasis; PsoBest = German Register on the Treatment of Psoriasis with Biologics and Systemics.

[a] Source: TWB (2015).

[b] Source: Ormerod et al. (2012).

[c] Source: Parisi et al. (2013).

[d] Source: Feldman et al. (2014).

[e] Source: IVDP (2015).

[f] Source: Iskandar et al. (2015).

[g] Source: based on a communication from BIOBADADERM, a number of patients between those of apremilast (65) and secukinumab (103) [data during 2017] is to be expected.

[h] Estimated proportion of annually eligible patients actually enrolled in the register each year: 10%, year 1; 30%, year 2; 40%, year 3; 35%, year 4; and 30% in subsequent years until the end of study period.

[i] Estimated proportion of annually eligible patients actually enrolled in the register each year is assumed to be 90%.

[j] Source: based on a communication from BADBIR, the proportion of annual eligible patients actually enrolled in the register each year is assumed to be 44%.

Patient recruitment into the targeted registers will be monitored periodically. If after 3 years from study start the number of patients in the targeted registers remains significantly lower than the estimate, the inclusion of additional patient registers in other countries will be explored. Based on the expected number of prescriptions, the next country with an established psoriasis register that would be considered is Italy.

Further, should enrolment in the registers remain low, the Applicant will consider as an alternative option the use of data from selected population-based health care databases. The following countries and databases will be considered conditional upon Skilarence launch and reimbursement approval:

- Germany—the German Pharmacoepidemiological Research Database (GePaRD)
- Italy—Health Search database
- Spain—the Information System for the Advancement of Research in Primary Care (Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària [SIDIAP]) database in Catalonia

9.6 Data Collection and Management

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all programmes. Each research partner will maintain any patient-identifying information securely on site according to internal standard operating procedures or guidance documents.

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed (e.g., storage on CD-ROM or DVD), with periodic backup of files to tape. Standard procedures will be in place at each research centre to restore files in the event of a hardware or software failure.

9.7 Data Analysis

Data analyses for the annual progress report will be adjusted as per data availability in each register and upon agreement by register custodians. For the three registers, the analyses will be the standard periodic analyses conducted at the routine fixed time points established by each register (i.e., PsoBest and BADBIR every 6 months, BIOBADADERM annually) and following the standards of the Manchester Template report (see example of BADBIR report template in Annex 4) as adapted by each register.

The following description is of the planned annual analyses that will take place, adjusted to data availability at each register:

- Description of the study cohorts at baseline using mean values and standard deviations for continuous variables and percentages for categorical variables (in BIOBADADERM, the conventional systemic cohort will consist of patients treated with methotrexate:
  - Demographics: age, sex
  - Specific baseline comorbidities at treatment start
  - Comedications at baseline, where available
  - Treatment for psoriasis prior to inclusion in the cohort
- Description of treatment course:
  - Number of patients and cumulative person-time of follow-up accrued in each study cohort
  - Number and percentage of patients who discontinued treatment in each cohort
  - Description of reasons for discontinuation
- Description of the safety endpoints (serious infections, serious opportunistic infections, PML, malignancies, all types of renal impairment) in each cohort:
  - Number of safety endpoints reported, number and percentage of patients with the safety endpoint, and cumulative patients with each type of event per 100 patient-years of exposure, by MedDRA SOC as described in Section 9.3.2.1.
- Description of all “other” SAEs and all AEs in each cohort, by MedDRA SOC

For each register, at the end of the study period, the following analyses will be conducted in addition to the analyses previously described, to the extent that is possible with the accrued number of patients and events:

- Description of the study cohorts at baseline:
  - Demographics: age, sex
  - Body mass index, smoking status, alcohol use
  - Specific baseline comorbidities at treatment start
  - Comedications at baseline, where available
  - Previous systemic psoriasis therapy
  - Type of psoriasis, psoriatic arthritis, years since psoriasis diagnosis, percentage of body surface area with psoriasis lesions, PASI score, PGA score, and DLQI score at treatment start
- Description of treatment course:
  - Number of patients and cumulative person-time of follow-up accrued in each study cohort
  - Number and percentage of patients who discontinued treatment in each cohort
  - Description of reasons for discontinuation

  - Dose of Skilarence at treatment initiation and first maintenance dose in three categories: above the recommended dose, below the recommended dose, and recommended dose, where available

- Analyses conducted for each primary safety endpoint:

  Incidence rates for patients initiating Skilarence and for patients initiating other conventional systemic therapies will be estimated overall and stratified by relevant factors measured at baseline (listed in the Variables section), at least by defined special patient populations (i.e., patients aged over 65 years; pregnant and lactating woman; patients with renal impairment, hepatic impairment, gastrointestinal disease, or preexisting infections and immunosuppressed patients) if the number of patients is sufficient. Person-time at risk for the calculation of the incidence rate of each primary safety outcome is described in Section 9.3.2.1.

    - In PsoBest, incidence rates will also be estimated for the group of patients treated with other FAEs.
    - In BIOBADADERM, incidence rates will be estimated for methotrexate and for other conventional systemic treatments

  - IRR estimates comparing Skilarence and other conventional systemic therapies will be calculated. Crude, stratified, and adjusted IRR estimates will be presented. Adjustment for relevant baseline characteristics will be performed through multivariable modelling if the number of patients is sufficient.

    - In PsoBest, IRR estimates comparing Skilarence and other FAE therapies will also be calculated. As in the main analyses, crude, stratified, and adjusted IRR estimates will be estimated.

  - Point estimates from pooled analysis of point estimates from the three registers: incidence rates, overall and stratified by selected factors, and IRRs adjusted for relevant factors.

- Depending on scientific interest and the distribution of the data, subsequent exploratory analyses may be performed
- Description of all “other” SAEs and all AEs in each cohort, by MedDRA SOC:
  - Number of each type of event reported
  - Number and percentage of patients with each type of event
  - Cumulative number of patients with each type of event per 100 patient-years

If informative censoring or nonrandom patterns of missing data are observed in the study, then appropriate statistical methods to account for this fact will be considered (e.g., selection models, joint modelling of the outcome and time to dropout) as a sensitivity analysis to determine the potential influence on the main findings of the study.

To address the possible confounding by indication, stratified subgroup analysis will be considered to account for disease severity, time since diagnosis of psoriasis, comorbidity at baseline, prior psoriasis therapy, and age.

9.8 Quality Control

Standard operating procedures or internal process guidance at each research centre will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

The following information about quality-control programmes at each register is in the public domain:

- PsoBest: A quality-control programme is applied at the performance levels of the central study management office of the German Centre for Health Services Research in Dermatology (CVderm), the participating centres, the patients, and by monitoring study centres. All the different quality-control procedures applied in PsoBest are regulated by standard operating procedures, which are evaluated at regular intervals. PsoBest undergoes checks to detect and prevent errors. The process is checked every 3 months to detect systematic errors. All the functions and goals of the employees at PsoBest are evaluated every 6 months. CVderm audits PsoBest during the follow-up. The scientific advisory board evaluates the quality and performance of PsoBest; supervises the planning, performance, and analysis phase; and makes essential strategic decisions. All study centres participating in PsoBest must fulfil the following quality characteristics: reports should be made only by trained dermatologists, centres should have adequate experience in all forms of psoriasis, and dermatologists should be familiar with the use of all questionnaires and disease severity instruments used. Case reports are checked for plausibility as soon as received. The quality of data recorded at the individual study centres is evaluated for plausibility. After an internal evaluation of data of questionable quality, measures to improve the process of data collection will be implemented in each study centre. The study centres reporting at least 10 patients or an SAE are routinely monitored (once a year) by specialised PsoBest personnel. The information about treatment and main outcomes from each patient with a reported SAE or AESI or pregnancy is verified. Additionally, the information collected from a randomly selected 10% of all other patients in the study centre is monitored, with a focus on SAEs, AESI, pregnancy, and all information on treatment and main outcomes. The registry documentation at each centre is also checked for completeness and accuracy.
- BIOBADADERM: All staff are trained before starting participation. We use a researcher manual that is updated as needed. Online continuous monitoring and yearly in situ monitoring to check the register data against the medical records of a random sample of patients is done. In addition, the electronic data capture system has automated filters to identify abnormal values and errors at data entry. An advisory board evaluates the quality and performance of BIOBADADERM in two annual meetings.
- BADBIR: A coordinated programme provides training to staff, and an online manual to guide the data collection and the use of data collection forms is available for participating dermatologists. Data undergo quality checks for inconsistencies at data entry. Data received are manually checked for completeness and errors. A predefined set of criteria is used to assess the validity of selected SAEs. To mitigate the potential for patients to be lost to follow-up or for adverse events to be missed during data collection, BADBIR can perform linkages of patients (through patient-identifiable data) to relevant national health care providers (NHS) to receive information about

mortality, malignancies, and inpatient hospital admissions. This linkage will continue after the formal follow-up of patients entered in the register is complete. All patient-identifiable information is encrypted and stored at the University of Manchester and only transferred to the relevant organisation for the purpose of linkage.

For RTI-HS, all key study documents, such as the analysis plan, abstraction forms, and study reports, will undergo internal quality-control review, senior scientific review, and editorial review.

For RTI-HS, an independent Office of Quality Assurance will perform audits and assessments that involve various aspects of the project, including but not limited to education and training documentation, data entry and data transfer procedures and documentation, and institutional review board documentation. Such audits will be conducted by the Office of Quality Assurance according to established criteria in standard operating procedures and other applicable procedures.

A quality-assurance audit of this study may be conducted by the marketing authorisation holder or the marketing authorisation holder's designees.

Appropriate data storage and archiving procedures will be followed (i.e., storage on CD-ROM and DVD), with periodic backup of files to tape. Standard procedures will be in place to restore files in the event of a hardware or software failure at each research centre.

9.9 Limitations of the Research Methods

There are several limitations derived from the use of patient registers. The main limitation is the low number of patients that might be included in the analysis. In this study, during the study period, patients treated with Skilarence will form one cohort, and patients treated with any other conventional (non-biologic) systemic therapy will form the comparator cohort. The Skilarence cohort is expected to be smaller than the other conventional (non-biologic) systemic therapies cohort. With a small sample size, some events with a very low incidence (e.g., PML, specific types of cancer) might not be detected or estimates will be of limited precision. In addition, some of the planned analyses might not be conducted in case of scarcity of data. We have conducted preliminary estimations of enrolment, but these are uncertain given the many assumptions in the estimation.

Participation and involvement in these registers is voluntary, and therefore, not all patients treated with Skilarence or other conventional systemic therapies will be included in the study. This may introduce a selection bias if certain subgroups of patients are routinely included in or excluded from the register or if participation in the registers is differential depending on the socioeconomic status (e.g., if participation is higher among more advantaged patients) or any other factor.

The participating registers have a predetermined length of follow-up, meaning that data about each individual patient will not be collected after the end of follow-up, which varies by register from 8 years in BIOBADADERM to 10 years in PsoBest and BADBIR. Patients can be lost to follow-up for several reasons, including not only determined end of follow-up in each register but also censoring due to lack of efficacy or inefficacy, recovery, or AEs and remission. Loss to follow-up could introduce selection bias if it differs by

treatment exposure. Appropriate statistical models will be applied if informative censoring or nonrandom patterns of missing data are observed in the study.

Information in the participating registers is collected by physicians and in BADBIR and PsoBest by patients. Information bias may also be introduced if routine follow-up of patients is influenced by the treatment they receive, which is possible with treatments that require close monitoring of biological parameters through laboratory tests.

Laboratory values are not collected in PsoBest and BIOBADADERM, and they may only be available and limited to specific parameters in BADBIR, which limits the ability to identify and follow-up outcomes of renal and hepatic function–related AEs. The follow-up of renal and hepatic function will be only captured through the reported AEs. There will be also differences in the way information on safety endpoints, exposure and covariates, and risk factors are collected. The quality of the data collected and the completeness of the data may limit identification of events and lead to underestimation of event rates and biased event-rate ratios towards unity if there is nondifferential misclassification. However, small differences between groups in misclassification of the endpoints or exposure may result in bias towards or away from unity in an unpredictable manner (Jurek et al., 2008). Poor completeness of data may also impact the ascertainment of covariates and therefore limit the ability to perform adjustments in the analyses to reduce potential residual confounding. Each of the proposed participant registers have established procedures to ensure the quality of data. However, all procedures target the evaluation of completeness and accuracy of the information reported to the registers; consequently, the ability to quantify the level of underreporting is limited.

Another limitation is related to differences in the enrolment of patients under treatment with Skilarence and other conventional systemic therapies in the three selected registers that may be influenced by physicians and patient preferences and different health care systems.

Finally, severity of disease is a possible source of confounding by indication (Salas et al., 1999). In this sense, the severity and duration of psoriasis should be controlled with stratification and in the final multivariable models to avoid residual confounding. Skilarence is prescribed for the treatment of moderate to severe chronic plaque psoriasis in adult patients in need of systemic therapy. The indication for the different treatments included in the comparator group should be similar. Nevertheless, small differences in prescribing practices in the study medications between countries or even between physicians may have an impact on our results.

9.10 Other Aspects

Approval by ethical committees or institutional review boards and/or any other required reviews of the study protocol by specific committees will be obtained in accordance with applicable national and local regulations.

The study will be conducted in accordance with the International Society for Pharmacoepidemiology's (ISPE's) *Guidelines for Good Pharmacoepidemiology Practices* (*GPP*) (ISPE, 2015) and in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2017). The ENCePP *Checklist for Study Protocols* (ENCePP, 2016a) has been completed (see Annex 2), and the study will be

registered in the European Union (EU) Post-Authorisation Studies (PAS) Register (ENCePP, 2018b).

The study is a PASS and will comply with the definition of the non-interventional (observational) study provided in the *Guideline on Good Pharmacovigilance Practice (GVP): Module VIII – Post-Authorisation Safety Studies* (EMA, 2017b). The study will comply with the nature of non-interventional (observational) studies referred to in the ICH harmonised tripartite guideline *Pharmacovigilance Planning E2E* (ICH, 2004). The study will comply with the study reporting requirements specified in Module VIII Section VIII.B.6.3.1. “Progress reports” and VIII.B.6.3.2. “Final study report” of the *Guideline of Good Pharmacovigilance Practices* (EMA, 2017b).

The research team and Almirall adhere to the general principles of transparency and independence in the ENCePP Code of Conduct (ENCePP, 2018a).

10 Protection of Human Subjects

This non-interventional observational study will use secondary data from targeted established psoriasis registers in various countries. Patients registered with PsoBest, BIOBADADERM, and BADBIR have previously consented to have their health data collected and stored in these registers and to be followed. Patients are treated as per their routine clinical care, and the study will not influence or dictate the administration of any specific study medication. No new informed consent is required to conduct this PASS in these registers.

11 Management and Reporting of Adverse Events/Adverse Reactions

Data on all AEs are collected by the registers as reported by participating physicians.

In BIOBADADERM, as required by local regulations, the physician communicates SAEs to the Spanish Pharmacovigilance System using an online tool linked to the register electronic data collection website.

In BADBIR, AE reports are reviewed and AEs are coded by pharmacovigilance experts using MedDRA; SAEs are reported to the corresponding product MAH upon receipt of the event report by the register, and a line listing of adverse drug reactions (ADRs) is provided every 6 months.

In PsoBest, participating physicians must report SAEs to CVderm within the first 24 hours after noticing. The SAE report should contain all available medical information (including laboratory results, hospital discharge letters, etc.). The reporting dermatologist is the person responsible for reporting SAEs to the competent health authority. CVderm is responsible for reporting SAEs (initial and follow-up) to the MAH of the product after plausibility has been evaluated and the event report has been confirmed to meet the minimum criteria. Line listings of AEs and SAEs are provided to the MAH every 6 months.

Based on current guidelines from ISPE (ISPE, 2015) and the EMA *Guideline on Good Pharmacovigilance Practices: Module VI – Management and Reporting of Adverse Reactions to Medicinal Products (EMA, 2017a)*, non-interventional studies such as the one described in this protocol, using secondary data, do not require expedited reporting of AEs or ADRs.

12 Plans for Disseminating and Communicating Study Results

The study protocol, study progress reports, and final study report will be included in regulatory communications in line with the Risk Management Plan, Periodic Safety Update Reports, and other regulatory reporting requirements. Study reports will be prepared using a template following the *GVP Module VIII* Section B.6.3 (EMA, 2017b).

In its *GPP*, ISPE contends that "there is an ethical obligation to disseminate findings of potential scientific or public health importance" (ISPE, 2015); for example, regarding results pertaining to the safety of a marketed medication: "…the marketing authorisation holder should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within two weeks after first acceptance for publication."

Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (ICMJE, 2017). When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology checklist will be followed (von Elm et al., 2008).

Almirall and the investigators will agree upon a publication policy allowing the principal investigator to independently prepare publications based on the study results, irrespective of data ownership. Almirall will be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication. Almirall and the research team are aware that Almirall should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within 2 weeks after first acceptance for publication (EMA, 2017b).

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Annex 1.
Collaborating Institutions

British Association of Dermatologists Biological Interventions Register, United Kingdom

- Prof. Chris Griffiths, BADBIR Chief Investigator

Fundación de la Academia Española de Dermatología y Venereología, Spain

- Dr. Ignacio García Doval, BIOBADADERM Scientific Coordinator

German Center for Health Services Research in Dermatology (CVderm), Germany

- Prof. Dr. Matthias Augustin, PsoBest Principal Investigator

Annex 2.
ENCePP Checklist for Study Protocols

Doc. Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: An Observational Post-Authorisation Safety Study of Skilarence in European Psoriasis Registers

Study reference number: Not yet assigned

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection*	☒	☐	☐	6
1.1.2 End of data collection†	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☐	☒	☐	6
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results	☒	☐	☐	6

Comments:

* Date from which information on the first study is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts.

† Date from which the analytical data set is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the Risk Management Plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g., cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g., incidence rate, absolute risk)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g., relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2
4.2.2 Age and sex?	☒	☐	☐	9.2
4.2.3 Country of origin?	☒	☐	☐	9.2
4.2.4 Disease/indication?	☒	☐	☐	9.2
4.2.5 Duration of follow-up?	☒	☐	☐	9.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g., current user, former user, non-use)	☒	☐	☐	9.3.2.1
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.1
6.3 Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g., HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.7,9.9

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.9
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g., healthy user bias)	☒	☐	☐	9.9
7.2.2. Information biases (e.g., misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates? (e.g., age, sex, clinical and drug use history, comorbidity, comedications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
9.3.3 Covariates?	☒	☐	☐	9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7
10.5 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Elena Rivero Ferrer, MD, MPH, FISPE

Date: 14 /June/2018

Signature: [redacted]

Annex 3. Operational Definitions

Table 10. Preliminary List of Target MedDRA Terms for Identification of Primary Safety Outcomes of Interest

Primary Endpoints	MedDRA Description RMP (Version 15.0)	MedDRA Description (Version 21.0)
All serious infections	▪ High-level group terms: – Viral infections disorders – Bacterial infectious disorders – Fungal infectious disorders – Mycobacterial infectious disorders – Protozoal infectious disorders ▪ High-level term: Infections NEC	Seriousness: Serious ▪ High-level group terms: – Viral infections disorders – Bacterial infectious disorders – Fungal infectious disorders – Mycobacterial infectious disorders – Protozoal infectious disorders ▪ High-level term: Infections NEC
Serious opportunistic infections	NA	Seriousness: Serious ▪ High-level terms: – Cryptococcal infections – Toxoplasma infections – Cytomegaloviral infections – Pneumocystis infections – Herpes viral infections – Candida infections – Atypical mycobacterial infections – Tuberculous infections ▪ Preferred terms: – Bronchopulmonary aspergillosis – Gastroenteritis cryptosporidial – Microsporidia infection – Gastroenteritis cryptosporidial – Microsporidia infection
PML	NA	▪ PT: Progressive multifocal leukoencephalopathy
All malignancies	▪ SMQ: Malignant or unspecified tumours	▪ SMQ: Tumours of unspecified malignancy
All renal impairments, including Fanconi syndrome	▪ SMQ: Acute renal failure ▪ HLT: Renal failure and impairment ▪ HLGT: Nephropathies	▪ SMQ: Acute renal failure ▪ HLT: Renal failure and impairment ▪ HLGT: Nephropathies

HLGT = high-level group term; HLT = high-level term; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; NEC = not elsewhere classified; PML = progressive multifocal leukoencephalopathy; PT = preferred term; RMP = risk management plan; SMQ = standardised MedDRA query.

Annex 4. Standard Periodic Report Example: BADBIR Report Template

BADBIR Company Report Template

1. Section 1 – Definitions and Notes

2. Section 2 – <*Biologic*> Patients

    - Demographics
    - Baseline Characteristics
    - Serious Adverse Events Reported Rates (example table provided)

3. Section 3 – Comparison Patients

    - Demographics
    - Baseline Characteristics
    - Serious Adverse Events Reported Rates (example table provided)

Example: Adverse Events Recorded (rates are per 1000 person years)

Event	Males		Females		Total	
	Events	Rate (95% CI)	Events	Rate (95% CI)	Events	Rate (95% CI)
Total Serious Infection						
Pneumonia						
Septicaemia						
Bone/Joint infection						
Opportunistic infection						
Other serious infection						
TB						
Respiratory (non-infection)						
Total cardiac disorders						
CHF (new or worsening)						
Myocardial infarction						
Other cardiac events						
CNS Disorders						
Demyelination						
Peripheral neuropathy						
Other CNS						
Skin (non cancer)						
Total haematologic events						
Aplastic anaemia						
Pancytopaenia						
Agranulocytosis						
Other dyscrasia						
Total malignant events						
Lymphoproliferative						
Lymphoma						
Myeloma						
Leukaemia						
Other Lymphoproliferative						
Skin Cancer						
Non Melanoma Skin Cancer						
Melanoma						
Other Skin Cancer						
Other malignant solid tumours						
Other malignant SAE						
Pregnancy						
Death						