

Non-Interventional Study Protocol

Study Short Title

**Evaluation of the sensitivity and specificity of a novel quality of life (QoL)
tool to assess the treatment satisfaction in psoriasis patients**

STUDY IDENTIFICATION No. 2020-A00652-37

Full Study Title

Evaluation of the sensitivity and specificity, compared to DLQI as a standard tool, of a novel QoL questionnaire (treat to the PSOriasis patient satiSfactiOn TARGET) among moderate to severe psoriasis patients treated with brodalumab (Kyntheum®)

GPP statement: *This Non-Interventional Study will be conducted in compliance with the Clinical Study Protocol, Good Pharmacoepidemiology Practices and applicable regulatory requirement(s).*

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APPENDICES**1. PSO-TARGET Component grid**

2 List of Abbreviations

ADR:	Adverse Drug Reaction
AE:	Adverse Event
CRF:	Case Report Form
CRO:	Contract Research Organization
DLQI:	Dermatology Quality of Life Index
HCP:	Healthcare Practitioner
IEC:	Independent Ethics Committee
IRB:	Institutional Review Board
LEO	LEO Pharma A/S and/or affiliates or representatives
MedDRA:	Medical dictionary for Regulatory Activities
NIS:	Non-Interventional Study
OE:	Other Experience
PASI:	Psoriasis Area and Severity Index
PRO:	Patient Reported Outcome
QoL:	Quality of Life



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LEO Pharma legal entity is the sponsor of the study and the Contract Research Organisation(s) (CRO) CLINACT is authorised by LEO to act on behalf of LEO. LEO Pharma 2 Rue René Caudron, 78960 Voisins-le-Bretonneux, France will be the Data Controller.

Contact and responsibilities of all parties contributing to the study, including all investigators, are detailed in a stand-alone document available upon request to LEO. For key contributors, e.g. national coordinating investigators, LEO will keep CVs and documentation regarding Conflicts of Interest and make such documentation available upon request from relevant parties, e.g. authorities, journals. LEO will keep a record of all relevant sponsor personnel. CLINACT will keep a record of all involved CRO personnel.

The following essential documents must be in the hands of LEO before the study is initiated at a site:

- Written agreement between LEO or CLINACT and the Study Site Responsible / Clinic / Hospital.
- Signed and dated protocol agreement and amendment agreements, if any, with the original signature of the Site Responsible.
- Patient Information Sheet and Informed Consent Form in local language (notified to / approved by Independent Ethics Committees (IECs).
- Written IEC / IRB approval.
- Competent Authority notification.
- Product liability insurance.
- LEO safety plan which is a three party agreement between Global safety, Safety contact person and the CRO on the handling of safety reporting



4 Abstract

Title

Evaluation of the sensitivity and specificity, compared to DLQI as a standard tool, of a novel QOL questionnaire (treat to the Patient satisfactiOn TARGET in Psoriasis patients) among moderate to severe psoriasis patients treated with brodalumab (Kyntheum®)

Rationale and background

The severity of psoriasis can be influenced by a great variety of factors including extent of the disease, lesions location and impact on quality of life. The current standard of care for psoriasis is focusing on the reduction of the skin symptoms as defined by the PASI, somewhat setting asides the patient's feelings in terms of which aspects of his/her life are affected by the disease. Despite the fact that multiple patient reported outcomes (PRO) questionnaires are available to evaluate the impact of the disease on patients' quality of life, only few items address the subjective impact of skin disease. Among the available PROs the Dermatology Life Quality Index (DLQI) is the most frequently used. It is a standardized tool designed to cover a broad range of dermatologic afflictions but lacks specificity towards the effect of psoriasis on quality of life. The DLQI is composed of ten questions grouped in 6 domains "symptoms and feelings", "daily activities", "leisure", "work/school", "personal relationships" and "treatment". Each answer is graded from 0 to 3. The DLQI score is calculated by adding the score of each question, resulting in a maximum score of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. A score higher than 10 indicates that the patient's life is being severely affected by their skin disease.

Because of its limitations, some patients cannot seem to completely restore a normal quality of life (e.g. DLQI 0-1) even though their reached a perfect PASI score (100). This phenomenon may be explained by the fact that the patient's own perception can be different from the physician's perspective and may have changed in time, between follow-ups. These are as many reasons as why it is highly difficult to accurately fathom the therapeutic expectations of the psoriasis patients. The standard tools currently in use are not able to assess the perception of the disease by the patient its evolution over time. In addition, it is widely recognized that alexithymia is more prevalent in the psoriasis patients than in the general population and patients with alexithymia appear to suffer higher psoriasis burden as they have more difficulties to express their expectations. Since patients struggle to recognize and verbalize their emotions, it can be useful and informative to offer patients a variety of verbatim in which



they can identify. PSO-TARGET is an exploratory observational, non-interventional study aiming to evaluate a novel approach of assessing psoriasis patients' satisfaction towards their biologic treatment from a quality of life standpoint by using a psoriasis-specific Quality of Life assessment grid.

Research question and objectives

The aim of this exploratory study is to evaluate the sensitivity and specificity of the PSO-TARGET QoL Component grid as part of a new approach for assessing the level of achievement of the psoriasis patient's therapeutic goal, identified by himself, after a treatment with Kyntheum®. This tool will be, if validated, used by physicians to devise a "Treat to patient satisfaction target" strategy that better suits their patients' expectations.

To construct this new questionnaire, the first step was to collect psoriasis patients' feedback on what is the aspect of their life that is the most impacted by the disease and which is the one they would want to improve the most. To this aim, a retrospective survey based on the recollection and experience from three clinical dermatologists (two French and one Belgian) of patient's expectations, has been conducted. The results of the survey have been used to analyse the type of expectations provided by the patients. Based on that analysis, the expert dermatologists generated a grid containing 12 therapeutic goals equally distributed into the four major psychometric components classically used in quality of life studies in patients with chronic diseases (physical, subjective, relational/social and therapeutic). The proposed verbatim was then reviewed by a psychologist to ensure that there was a balance between the proposals; i.e. the vocabulary used was neutral enough not to guide the choices. This first step has therefore given rise to a QoL component grid that will be administered to the patients prior to the initiation of a systemic treatment (Kyntheum® / brodalumab) to set up a main objective for the upcoming treatment. At 12-16 weeks the patient will be asked to rate his/her level of satisfaction in regard to the treatment objective defined prior to treatment initiation using a four-point Likert scale ("very satisfied", "satisfied", "unsatisfied", "very unsatisfied"). In order to evaluate the sensitivity and specificity of, the PSO-TARGET QoL component grid, the patient will be asked to fill in, prior the treatment introduction and during the follow up visits, the DLQI questionnaire. The primary objective of the study will be to estimate the level of concordance of this satisfaction level based on the PSO-TARGET QOL tool and the reference method in Quality of Life for psoriasis patients; i.e. the DLQI, at the same time point. This aim will be reached by comparing, at 12-16 weeks, the DLQI and the satisfaction level given by patients in regard to their own treatment objective defined at baseline using the PSO-TARGET



QoL component grid. True Positive (TP), False Positive (FP), True Negative (TN) and False Negative (FN) will be defined using a contingency table. These quantitative variables will be used to calculate the sensitivity (proportion of actual satisfied patients that are correctly identified as such) and specificity (proportion of actual unsatisfied patients that are correctly identified as such) of the PSO-TARGET QoL Component grid, compared to the quality of life given by the DLQI. If these metrics reach a certain threshold (85%), the PSO-TARGET QoL component grid will be considered for additional studies in order to validate it at a larger scale and further demonstrate it is as much sound in assessing the patients' quality of life as the DLQI.

Because of the fact that alexithymia is highly prevalent in psoriasis patients, the grid will be administered to the patient after he/she had spontaneously expressed his/her treatment expectations. This should help the patient to narrow down the specific goal where his/her expectation belongs. In addition, as part of a secondary objective the treating physician will also choose an item from the table based on what he/she perceives in terms of patient's expectations without disclosing it to the patient. This will allow us to evaluate the level of accordance between the physician-chosen and the patient-chosen therapeutic goal. As another secondary endpoint, the level of achievement of the therapeutic goal will be assessed at 12/16 weeks and followed-up for 52 ± 4 weeks. Patients scoring the treatment as "satisfied or very satisfied" will be considered as having achieved their therapeutic goal. Another endpoint of interest (secondary) will be to assess, after 12/16 weeks of treatment, if the patient chooses a new therapeutic goal, different from the one he initially defined.

It is important to note that, this study being observational, none of the visits (baseline and follow-ups) are specific to the trial but part of the dermatologists' standard of care in both countries (France and Belgium). In addition, in order to limit variability in terms of treatment profiles (dosage and administration schedule) and thus to keep the study population as homogenous as possible, it has been decided to include only patients treated by Kyntheum®, in other terms Kyntheum® treatment is an accessory to the study but PSO-TARGET will not assess Kyntheum® efficacy *per se*.

The study objectives are the following:

Primary objective:

Assess at week 12/16, post biologic treatment, the sensitivity and the specificity, compared to DLQI as a standard tool, of the PSO-TARGET QoL component grid as a novel approach aiming to evaluate the patients' satisfaction with regard of their treatment.



Secondary objectives:

- Evaluate at week 12/16, post Kyntheum® treatment, the percentage of patients who has achieved the main treatment goal they identified in the QoL component grid at baseline.
- Identification of predictive factors (among baseline characteristics) of the achievement of the main treatment goal;
- Evaluate the level of agreement between the dimensions reported by the patient and by the treating physician;
- Evaluate at 52 weeks the percentage of patients for whom the therapeutic objective initially achieved at the 1st follow-up visit is still maintained;
- Evaluate the percentage of patients who change their therapeutic objective after 12/16 weeks of treatment;
- Follow the evolution of the PASI score (at 12/16 and 52 weeks);
- Level of accordance between PASI 90/100 and the satisfaction level in regard to the therapeutic objective set by the PSO-TARGET QoL Component grid;
- Follow the evolution of the DLQI score (at 12/16 and 52 weeks).

Study design

PSO-TARGET is an observational, non-interventional, prospective, multicentric, international, European study requiring no change in the patients' standard of care (RIPH3 in France).

Population

Adult patients suffering from moderate to severe *psoriasis vulgaris* for whom the dermatologist decided to prescribe a treatment with Kyntheum®.

Variables**Primary endpoint**

- At 12/16 weeks, level of concordance between the satisfaction level in regard to the therapeutic objective set by the PSO-TARGET QoL Component grid and the DLQI in assessing the impact of the treatment on the patients' quality of life.

Secondary endpoints

- At week 12/16, post Kyntheum® treatment, the percentage of patients who achieved the main treatment goal identified by the patient himself in the QoL component grid at



baseline. The therapeutic objective achievement is defined as “satisfied” or “very satisfied” response on 4 points Likert scale.

- Level of concordance between the satisfaction level in regard to the therapeutic objective set by the PSO-TARGET QoL Component grid and the DLQI at the 2nd follow-up visit (52 ± 4 weeks.).
- Research of predictive factors (among baseline characteristics) of the achievement of the main treatment goal.
- Percentage of agreement between the physician-reported and the patient-reported dimensions at the first follow-up visit.
- Rate of patients having changed objective at the 1st follow-up visit (12/ 16 weeks).
- Percentage of patients who have maintained at 52 ± 4 weeks the level of satisfaction achieved at the 1st follow-up visit.
- PASI Scores at baseline, at the 1st follow-up visit (12/ 16 weeks), at the 2nd follow-up visit (52 ± 4 weeks.).
- Level of accordance between PASI 90/100 and the satisfaction level in regard to the therapeutic objective set by the PSO-TARGET QoL Component grid.
- DLQI Scores at baseline, at the 1st follow-up visit (12/ 16 weeks), at the 2nd follow-up visit 52 ± 4 weeks.

Data sources

Patients’ data will be collected at day 0, at the 1st follow-up visit (12/16weeks) and at the 2nd follow-up visit at 52 ± 4 weeks according to the physician’s practice.

As a prospective study, the following data will be collected during the patient visit: disease history, concomitant treatments, previous anti psoriatic treatment and adverse events. In addition, the following study specific data will be collected: disease severity (PASI score), quality of life questionnaires (DLQI, PSO-TARGET component grid).

Study size

The main criterion is the sensitivity of the PSO-TARGET tool (percentage of patients who consider their target objective as being achieved after 12/16 weeks of treatment as defined by a “satisfied or very satisfied” response, assessed on a 4 points Likert scale, among patients with a DLQI total score of 0 or 1).

The sample size calculation is based on the following hypotheses :



- ✓ Sensitivity : 90%
- ✓ Absolute precision : 10%
- ✓ Type I error : 5%
- ✓ Power at 80%
- ✓ Prevalence: 80% (estimated rate of patients with a DLQI 0-1 after 12 weeks of treatment).

Based on these hypotheses, the sample size needed is estimated at 134 evaluable patients.

Assuming 10% of patients will not be evaluable on main criterion, **150 patients have to be included.**

Data analysis

Analysis of the primary endpoint

The performance of the PSO-TARGET QoL component grid to assess the treatment impact on the patients' quality of life will be determined by calculating the sensitivity and specificity of the grid compared to the DLQI (reference). The grid will be validated if both the specificity and sensitivity parameters reach the 85% threshold.

Milestones

Regulatory Submissions: Q2 2020

Start of data collection Q3 2020

End of data collection Q2 2022

Final report Q4 2022

5 Amendments and Updates

None



6 Milestones

Planned dates for study milestones are indicated in the table below:

Milestone	Planned Date
Start of data collection	Q3 2020
End of data collection	Q2 2022
Final study report	Q4 2022

The start of the study is defined as the date on which the first information on a study patient is recorded in the study dataset. LEO will ensure that End-of-Data Collection (End of Study) notification is submitted to the concerned authorities and IECs for each site, for each country and for the complete study.

Based on upcoming knowledge, LEO might choose to terminate the study prematurely. In such case the Committee(s), study sites, IECs and authorities will be informed promptly.

7 Rationale and Background

Psoriasis is a chronic, immune-mediated inflammatory skin disease. Clinical manifestations of psoriasis can be of multiple forms, including, among others, plaque psoriasis, guttate psoriasis, palmoplantar psoriasis, and pustular psoriasis (Lebwohl, 2018). Psoriasis is characterized by an abnormal keratinocyte proliferation in the interfollicular epidermis along with an infiltration of antigen-presenting cells and release of pro inflammatory cytokines, leading to a local inflammation (Ippagunta et al., 2016; Lowes et al., 2007). The aetiology of the disease is not fully understood, but a number of risk factors are recognized, including family history and environmental risk factors, such as smoking, stress, obesity, and alcohol consumption (Huerta et al., 2007). The prevalence of psoriasis is difficult to evaluate with precision but is estimated around 2-4% in western countries (Gelfand et al., 2005; Kurd and Gelfand, 2009; Stern et al., 2004). In France, the prevalence of psoriasis is estimated to 4,4 % (Richard et al., 2018). Psoriasis causes considerable psychosocial disability and has a major impact on patients' quality of life (Krueger et al., 2001).

The severity of psoriasis can be influenced by a great variety of factors including extent of the disease, inflammation, lesions location and impact on quality of life. As those factors can fluctuate over time, so can the intensity of the disease and more importantly the patient's perception of his/her affliction. The current standard of care for treatment of psoriasis is



primarily focusing on the reduction of the skin symptoms as defined by the Psoriasis Area Severity Index (PASI), somewhat setting aside the patient's feelings in terms of which aspects of his/her life are affected by the disease. Indeed, a multinational study has already shown that a discrepancy exists between the physician's assessment of the disease severity and the patient's (van de Kerkhof et al., 2015). This could be, at least partially, explained by the use of standardized tools, by the physician which not necessarily take into consideration the patients therapeutic expectation which could sometimes be a subjective parameter. (van de Kerkhof et al., 2015). Currently, the higher efficacy observed with new biologics means that PASI 90 or even PASI 100 response are increasingly being considered as a new treatment goal (Daudén et al., 2016; Kerdel and Zaiac, 2015; Lebwohl et al., 2015). However, other quality of life aspects of chronic affections such as psoriasis that are not being assessed by tools like the PASI, must not be overlooked Multiple patient reported outcomes (PRO) questionnaires are available to evaluate the impact of the disease on patients' quality of life. Among the available PROs, the Dermatology Life Quality Index (DLQI) is the most frequently used (Puig et al., 2017). It is composed of ten questions grouped in 6 domains "symptoms and feelings", "daily activities", "leisure", "work/school", "personal relationships" and "treatment". Each answer is graded from 0 to 3. The DLQI is calculated by adding the score of each question, resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. A score higher than 10 indicates that the patient's life is being severely affected by their skin disease (Finlay and Khan, 1994). However, the DLQI is a standardized tool which missing potentially some quality of life specific issues for psoriasis patient. Consequently, among patients, some cannot seem to completely restore a normal quality of life (DLQI 0-1) even though they reached a perfect PASI score (100). This phenomenon may be explained by the fact that the patient's own perception can be different from the physician's perspective and may have changed between follow-ups. Although, the Patient Benefit Index has been devised to allow the patient to weigh the therapeutic goals in order to define which ones are the most important for him/her (using a 4 points Likert Scale, (Augustin et al., 2008)), it is not discriminatory enough towards the patient's principal expectation (Feuerhahn et al., 2012). In addition, it is widely recognized that alexithymia (difficulty to express emotion) is more prevalent in the psoriasis patients than in the general population and psoriasis patients with alexithymia appear to suffer higher psoriasis burden as they have more difficulties to express their expectations (Sampogna et al., 2017). Since these patients struggle to recognize and verbalize their emotions, it can be useful and informative to offer patients a variety of verbatim in which they can identify. Taken together these elements plea for a novel approach that take more into consideration the patient's expectations prior to treatment initiation and not only



the dermatologist symptomatic approach. We therefore believe that it is of importance to assess the 4 components of quality of life usually impacted in case of chronic disease as defined by Chassany (Chassany, 2003; Forestier et al., 2019), before initiating the systemic treatment, in order to define better therapeutics goals in an holistic approach. It is necessary to assess this new approach in a homogenous population, thus only patients starting a biologic treatment by Kyntheum® at the inclusion in the study will be enrolled. Indeed, satisfaction towards a treatment may be influenced by several factors including administration regimen.

The aim of this study is to evaluate, compared to the DLQI as a standard tool, the sensitivity and specificity of the PSO-TARGET QoL Component grid as a new QoL questionnaire for assessing the level of satisfaction of the psoriasis patients in achieving the therapeutic goal, identified by himself, after a biologic treatment. This study is the first step of an evaluation process aiming to validate the PSO-TARGET QoL Component grid. Ultimately, this tool will be used by physicians to devise a “Treat to patient satisfaction target” strategy that better suits their patients’ expectations. To construct this new questionnaire, the first step has been to collect psoriasis patients’ feedback on what is the aspect of their life that is the most impacted by the disease and which is the one they would want to improve the most. To this aim a retrospective survey based on the recollection and experience from 3 clinical dermatologists (2 French and 1 Belgian) of patient’s expectations, was conducted. The results of the survey have been used to generate a table containing 12 treatment goals equally distributed into the 4 major components classically used in quality of life studies in patients suffering from chronic diseases (physical, subjective, relational/social and therapeutic) (Chassany, 2003; Forestier et al., 2019). The proposed verbatim was then reviewed by a psychologist to ensure that there was a balance between the proposals; i.e. the vocabulary used was neutral enough not to guide the choices. This component grid will be administered to the patients prior to the initiation of a systemic treatment (Kyntheum® / brodalumab) to set up the main therapeutic objective (1 out of 12) fitting with his priority expectation from the upcoming treatment. The patient will only have access to the 12 treatment goals but not to the category headings. Because of the fact that alexithymia is highly prevalent in psoriasis patients, the grid will be submitted to the patient after he/she had been asked by the physician to express spontaneously his/her treatment expectations. This should help the patient to narrow down the item where his/her expectation belongs. At the 1st follow-up visit (12/16 weeks), the level of achievement will be assessed using a 4 points Likert scale (“very satisfied”, “satisfied”, “unsatisfied”, “very unsatisfied”). In order to evaluate the sensitivity and the specificity of the PSO-TARGET QoL component grid, the primary objective of the study will be to estimate the



level of concordance of this satisfaction level and the overall quality of life as defined by the DLQI at the same time point. It is important to consider that systemic treatment by Kyntheum® is an accessory to the study but the objective of the PSO-TARGET is not to evaluate Kyntheum® efficacy.

As part of secondary objectives, in parallel to that initial assessment by the patient, the physician will tick on the grid what would be his patients therapeutic goal based on what he knows/understands from the patient's disease history and therapeutic desires. At the time of his/her assessment, the physician will be blinded of the patient's choice of therapeutic goal. The accordance between the physician-chosen and the patient-chosen dimensions will be analyzed. The 12 items of the tool will be pooled and analysed by component (physical, subjective, relational and therapeutic). At 52 weeks, among other secondary endpoints, the maintenance of the level of achievement of the initial objective observed at the 1st follow-up visit, will be assessed.

One of the innovative aspects of this exploratory observational study will be the administration of a psoriasis-specific quality of life component grid containing 12 treatment objectives grouped in the 4 quality of life components/dimensions usually impacted in patients suffering from chronic diseases (Chassany, 2003; Forestier et al., 2019). Those dimensions accounting for the burden to bear when suffering from a chronic disease are the following: Physical, Subjective, Relational/Social and Therapeutic. Each dimension will include 3 patient's therapeutic goal based on dermatologists' clinical experience and reviewed by an expert on psychometric tools.

This is an exploratory study, a first step to assess the interest of the PSO-TARGET component grid. If the sensitivity and specificity reach an acceptable threshold (85%), the potential of the PSO-TARGET grid will be considered for validation in larger clinical studies. Indeed, more studies will be needed to test other attributes in order to fully validate the PSO-TARGET grid as an alternative to the DLQI for QoL assessment. Once the PSO-TARGET component grid is validated, it will prove to be a useful tool for a better design of a therapeutic objective from the physician and thus a better care brought to the patient which should improve the patient's satisfaction and treatment adherence.



8 Research Question and Objectives

8.1 Primary Objective

The primary endpoint will be the evaluation at week 12/16 of the sensitivity and the specificity, compared to the DLQI as a standard, of the PSO-TARGET QoL component grid to assess the level of satisfaction of patient achieving the therapeutic goal, identified by himself.

The therapeutic objective will be considered as achieved if the patient gives the responses “Satisfied” or “Very Satisfied” on the Likert scale. The response will then be compared to the DLQI score at 12/16 weeks.

8.2 Secondary Objectives

- Evaluate the percentage of patients who consider their target objective as being achieved after 12/16 weeks of treatment as defined by a “satisfied or very satisfied” response.
- Level of concordance between the satisfaction level in regard to the therapeutic objective set by the PSO-TARGET QoL Component grid and the DLQI at the 2nd follow-up visit (52 ± 4 weeks.).
- Evaluate the level of agreement between the dimensions reported by the patient and by the treating physician at baseline.
- Follow the degree of completeness of the main treatment goal identified at baseline after 52 weeks.
- Follow evolution of the PASI score (at 12/16 and 52 weeks).
- Level of accordance between PASI 90/100 and the satisfaction level in regard to the therapeutic objective set by the PSO-TARGET QoL Component grid.
- Follow evolution of the DLQI score (at 12/16 and 52 weeks).
- Evaluate the rate of patients who change their therapeutic objective after 12/16 weeks of treatment.

9 Research Method

9.1 Study Design

9.1.1 Eligibility criteria

The inclusion criteria are the following:

- Age > 18 years



- Patient for whom the dermatologist decided to initiate a treatment by Kyntheum® according to SmPC.
- Patient who signed an informed consent.

The following non-inclusion criteria will be applied:

- Vulnerable subjects according to the law;
 - pregnant, parturient or breast feeding women;
 - deprived of their freedom by administrative, medical or legal decision or who is under trusteeship/guardianship;
 - legally protected, or unable to express their consent to participate;
 - With no affiliation to a social security system;
- Psychologically/linguistically unable to express their consent to participate;
- With an hypersensitivity to at least one of the excipients of Kyntheum®;
- Participating at the same time in another clinical trial.

9.1.2 PSO-TARGET Quality of Life Component grid.

As a first step to construct the component grid, a retrospective survey based on the recollection and experience from 3 clinical dermatologists (2 French and 1 Belgian) of patient's expectations, has been conducted. The results of the survey have been used to generate a grid containing 12 therapeutic goals equally distributed into the 4 major psychometric components classically used in quality of life studies in patients suffering from chronic diseases (Chassany, 2003; Forestier et al., 2019). These four dimensions (cf table 1) are the following:

- **Physical:** autonomy, physical capabilities, ability to perform daily activities;
- **Subjective:** linked to experienced emotion, anxiety, well-being;
- **Relational/social:** with family, friendship or professional environment, engaging personal relationships, involvement in social or leisure activities;
- **Therapeutic:** linked to treatment, for ex. treatment-/care-related discomfort.

The investigators participating to the study will agree to implement this table as part of their standard of care along with the DLQI questionnaire.

Table 1: Quality of Life (QoL) component grid

Physical	Subjective	Relational/ social	Therapeutic
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Not be limited/handicaped by the pain	Think less or not at all about the disease	Spend quality time with family, friends or colleagues	Need to think less about treatment and care
Do not feel any functional discomfort (itching, rash) in my daily activities	Do not feel any anxiety from the disease	Not caring about what people think about me	Encounter very few, if any, drug discomfort
Have freedom of movement and activities	Feel serene, have peace of mind	Have a fulfilling intimate life	To be cured quickly

This grid will be administered to the enrolled patients after signature of the informed consent. The patient will be requested to identify what would be his/her main treatment objective. Only one item from the list will be picked by the patient. The investigator must not influence the patient into choosing a specific component to the table. The patient will have a grid with 12 proposals in front of him/her and will not be aware of the dimensions to which the proposals relate. The four dimensions typically described in chronic diseases will be considered only for analysis, but not submitted to patients. The patient will be given some space and time to choose the component without any help or supervision from the investigator. This is requested in order to avoid social desirability, defined as the tendency of some respondents to report an answer in a way they deem to be more socially acceptable than would be their "true" answer. The patient will then conceal his/her response in a provided envelope without revealing the chosen component to the physician.

In the meantime, the treating physician will identify the therapeutic objective that is supposedly the most important for his patient, based on his/her discussion with him. The physician-reported component will be concealed in a separate envelope and compared with the patient-chosen component during the analysis of the secondary endpoints.

As the primary endpoint of the study, the level of achievement of this therapeutic goal at 3 months (12/16 weeks) will be assessed by a 4-points Likert scale (Very Unsatisfied; Unsatisfied; Satisfied; Very Satisfied), and compared to the DLQI scoring classes.

9.1.3 Dermatology Quality of Life Index (DLQI)

The DLQI is designed to measure the health-related quality of life of adult patients suffering from a skin disease. It can be administered in patients aged 16 years and over and takes only few minutes to complete. The DLQI consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their health-related quality of life over the last week. It is not specific to psoriasis and is the most frequently used patient reported



outcome measure in randomised controlled trials in dermatology in general and in psoriasis more specifically (Cardiff University, 2019; Puig et al., 2017).

The DLQI is composed of ten questions grouped in 6 domains “symptoms and feelings”, “daily activities”, “leisure”, “work/school”, “personal relationships” and “treatment”. To each question the patient will have the followings choices: “Very much”, “A lot”, “A little”, “Not at all” or “not relevant”

Each answer is graded from 0 (“not relevant”, “not at all” or not answered) to 3 (“very much”). The DLQI is calculated by adding the score of each question, resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. A score higher than 10 indicates that the patient's life is being severely affected by their skin disease (Finlay and Khan, 1994).

More specifically, the total score will be divided into the following subcategories:

- 0-1 = no effect at all on patient’s life;
- 2-5 = small effect on patient’s life;
- 6-10 = moderate effect on patient’s life;
- 11-20 = very large effect on patient’s life;
- 21-30 = extremely large effect on patient’s life.

9.1.4 Limitation of bias

In order to limit bias, the sensitivity and specificity analysis need to be performed on a population as homogenous as possible. To this end, only patients treated with brodalumab (Kyntheum®) will be enrolled. By doing so we will limit the bias due to different treatment profiles (schedule of drug administration....). However, Kyntheum® efficacy will not be assessed during the study.

9.1.5 Study Schedule

The enrolment period is expected to be 5 months. After the patient’s individual treatment plan has been decided, he/she will be approached for informed consent to participate in the study and deliver data to use for national and pooled analysis.

Investigators are expected to enter data into the site specific part of the CRF at baseline and at any patient contact throughout the duration of the study. In order to complete and sign-off the CRF, a medical record may be used as source for historical data.

Visits will be according to local clinical practice and not decided in advance by the study protocol.



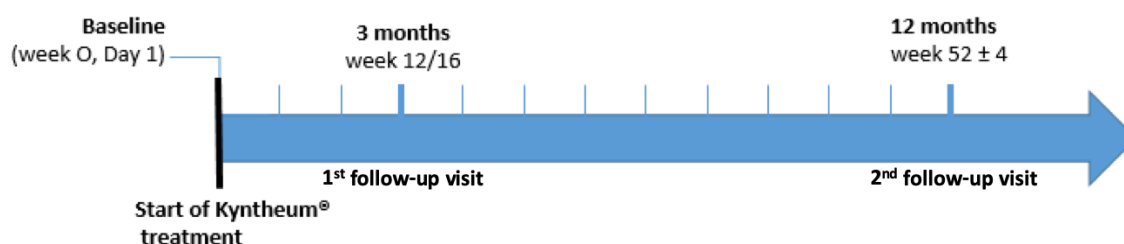
Relevant data from every visit within 52 weeks after baseline will be collected.

For analysis the following applies:

Visits that falls within week 12/-16 weeks are proxy for visit at 3 months. If more than one visit within this period, the visit closest to week 16 will be used for analysis.

Visits that falls within week 48-56 weeks are proxy for visit at 12 months (52 weeks \pm 4) .If more than one visit within this period, the visit closest to week 52 will be used for analysis.

The study design is the following:



The study will enrol consecutive patients planned to receive Kyntheum® and fulfilling the eligibility criteria. The assignment of the patient to Kyntheum® must not be decided in advance by the trial protocol, but must fall within current practice, and the prescription shall be clearly separated from the decision to include the patient in the study. The visit schedule is defined by the standard of care as there is no extra mandatory visits related to the participation in the study. Patients must be informed about the study and asked for consent to use their data, and patients willing to participate be enrolled.

9.1.6 Definition of a non-interventional study

The study is a 'non-interventional study' as defined for drug studies in Directive 2001/20/EC (European Commission, 2001) with primary data collection and will follow the guidelines for Good Pharmacoepidemiology Practices (Public Policy Committee, 2016).

This means that:

- The medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation;
- The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study



- No additional diagnostic or monitoring procedures are applied to the patients. Interviews, questionnaires, blood samples and patient follow-up may be performed as part of normal clinical practice.
- Epidemiological methods are used for the analysis of collected data.

9.2 Setting

The study is planned to be conducted in approximately 25 sites in 2 countries. Investigators will be clinical dermatologists. Each participating site is expected to include in average 5/6 patients. In case of slow recruitment in some sites, the other sites will be allowed to enrol up to 10 patients. Inclusion requires that Kyntheum® is prescribed in accordance with the approved terms of the marketing authorization in the country and that none of the stated contraindications apply.

Caution should be taken by the treating physician concerning any precautions, warnings and potential drug interactions stated in the product label.

Patients should be included in the study only once.

The study aims to involve sites and investigators that are representative for HCPs that prescribe biologics to patients suffering from *psoriasis vulgaris*. Sites can be hospital (university, private, public) dermatology departments, private dermatology clinics, and all sorts of general practices. Sites where patients are prescribed Kyntheum®, but for continuation of care are routinely referred to a different site without access to prescribe Kyntheum®, should not be selected for this study.

Information about the PSO-TARGET study should be given after the decision is made to treat the patient with Kyntheum®. It will be emphasized that the participation study will not condition the patient treatment and will not alter the visit schedule defined by the standard of care (3 and 12 months). After enrolment (i.e. signature of the Informed Consent Form), the physician will provide the patient with the QoL component grid along with the DLQI questionnaire. After having explained the purpose of the table in regards to the study, the physician shall give the patient enough time to reflect on which component is the most important for him/her without influencing him/her. Both questionnaires will be answered after this reflection period.



9.3 Variables

The following data will be collected from the patients' medical records and reported on the CRF by the investigator.

Consent

- Unique Study subject number (ISO three letter Country Code, followed by site number within country and consecutive patient number within site)
- Date of Informed Consent (dd.MMM.yyyy)
- Date of first case report recording (dd.MMM.yyyy)

Demographics

- Month/Year of Birth (MMM.yyyy)
- Gender (Male/Female)
- Weight (kg)
- Height (cm)

Medical History

- Date of diagnosis of psoriasis (dd.MMM.yyyy)
- Location of Psoriasis (List: scalp, nail, body, joint involvement, genital or intimate psoriasis, other)
- Body Surface Area (xx%)
- Commonly associated comorbidities (List: cardiovascular diseases, diabetes, hypertension, depression, psoriasis arthritis, inflammatory bowel disease, other)
- Smoking habits (never, active with pack years, not active with pack years and years since stopped)
- Alcohol consumption (never, occasionally or regularly with number of days/week, number of drinks per day when alcohol is used)
- Prior psoriasis treatment and posology + reason for discontinuation of the last therapy administered
- Standard occupational category.

Psoriasis treatments during study period



- Study treatment & co-medications (product name, formulation, dose, number of prescribed packages, package size)
- Date of treatment initiation
- Date of discontinuation (dd.MMM.yyyy)
- Reason for discontinuation (noncompliance, adverse event, requirement for alternative therapy, death, pregnancy, other)

Severity/effectiveness

- Psoriasis area and severity index (PASI)

Patient Reported Outcome

- Dermatology Life Quality Index (DLQI) score
- PSO-TARGET QoL component grid

The collected data are presented in the following flow chart of the study :



Reporter	Data to be collected	Base-line Visit (Day 0)	3 months Visit (week 12-16)	12 months visit (week 48-56)
Investigator	Unique Study subject	X		
	Month/Year of Birth	X		
	Gender	X		
	Weight	X		
	Height	X		
	Date of diagnosis	X		
	Location of Psoriasis	X		
	Body Surface Area	X		
	Commonly associated comorbidities	X	X	X
	Smoking habits	X		
	Alcohol consumption	X		
	Prior psoriasis treatment	X		
	Psoriasis treatment during study period	X	X	X
	Date of discontinuation of psoriasis treatment during study period		X	X
	Reason for discontinuation of psoriasis treatment during study period		X	X
	PASI	X	X	X
	QoL component grid	X	X	X
Patient	DLQI	X	X	X
	PSO-TARGET QoL component grid	X	X	X

9.4 Data Source

Investigator will complete the CRF with assessments and information according to the protocol. In addition, participants (patients) will be asked to enter data about their psoriasis symptoms and their Quality of Life, during the data collection period.

The below described scores will be mandatory:

Psoriasis Area and Severity Index (PASI) is the most widely used tool for the measurement of severity of psoriasis in clinical research. PASI combines the assessment of the severity of lesions and the area affected into a single absolute score in the range 0 (no disease) to 72 (maximal disease).



The **Dermatology Quality of Life Index (DLQI)** is well recognized Quality of Life questionnaire in psoriasis and capture a combination of symptoms, impact on daily routines, and feeling of stigmatization. It is a simple 10-question validated questionnaire that has been used in over 40 different skin conditions in over 80 countries and is available in over 90 languages. Its use has been described in over 1000 publications including many multinational studies. It is recommended to provide indirect measure of disease severity and is well used in studies on psoriasis and mentioned in the UK-treatment guideline (for details, see section 9.1.3).

The PSO-TARGET QoL component grid is a novel tool designed using a retrospective survey based on the recollection and experience from 3 clinical dermatologists of patient's expectations. It contains 12 therapeutic goals equally distributed into the 4 major psychometric components classically used in quality of life studies in patients suffering from chronic diseases (Chassany, 2003; Forestier et al., 2019). These four dimensions are: physical, subjective, relational/social and therapeutic. It has never been used before since it was designed for the PSO-TARGET study. Each patient will be required to pick only one item in the grid as his/her main therapeutic goal (see section 9.1.2). Treatment satisfaction in regards to the chosen component will be assessed at 12/16 weeks and 52 weeks by a 4 points Likert Scale and the level of concordance will be compared to DLQI scoring classes (described in section 9.1.2).

9.5 Study Size

The main criterion is the sensitivity of the PSO-TARGET tool (percentage of patients who consider their target objective as being achieved after 12/16 weeks of treatment as defined by a "satisfied or very satisfied" response, assessed on a 4 points Likert scale, among patients with a DLQI total score of 0 or 1).

The sample size calculation is based on the following hypotheses:

Sensitivity: 90%

Absolute precision : 10%

Type I error : 5%

Power at 80%

Prevalence: 80% (estimated rate of patient with a DLQI 0-1 after 12 weeks of treatment)

Hypothesis :



$H_0 : Se = Se_0$

$H_1 : Se = Se_1 > Se_0$

With Se =sensitivity, $Se_0=0.8$ and $Se_1=0.9$

Using the binomial probability formula, the sample size necessary to meet both a significance level and a power requirement may be found by solving the following two equations simultaneously :

Significance level $B (s_1 > s_\alpha | n_1, Se_0) = \alpha$

$B (s_1 > s_\alpha | n_1, Se_1) = 1 - \beta$

Where n_1 : patients with a DLQI 0-1, s_1 : patients with a DLQI 0-1 and a positive test outcome

With $\alpha=0.05$ and $1 - \beta=0.8$

To obtain n , n_1 is inflated by the prevalence P (rate of patients with a DLQI 0-1 = 80%), to obtain $n = n_1 / P$

The software used is PASS version 12, using the Li and Fine method (Li and Fine, 2004).

Based on these hypotheses, the sample size needed is estimated at 134 evaluable patients.

Assuming 10% of patients will not be evaluable on main criterion, **150 patients have to be included.**

9.6 Data Management

The Study Site will receive data collection tools (CRFs, questionnaires) from CLINACT. Whenever possible, complete data sets should be entered. Text field entries and any data collected on paper should be legible and follow the requested language standard.

The Study Site Responsible must sign off the complete data set reported by the site for each patient, confirming the collected data. Adverse Event and Other experiences reported according to section 11 should be signed off separately by a physician involved in the study. A causality evaluation should always be provided.

Data Management will be carried out according to a Data Management Plan which will be written and approved before the design of the study database is finalized. The data management provider should approve all data formats before the data collection tools are made available to the sites.

If the written informed consent of a patient is known not to be available in spite of it being required, data for this patient is not entered into or is deleted from the database.



If a patient is erroneously included in the study more than once only the data relating to the first inclusion will be kept in the database and be available for analysis. Data from later inclusions will be transferred to the first dataset when relevant, i.e. if collected within the time frame of the first follow-up period.

If a patient is included in the study in spite of not being treated according to the approved terms of the marketing authorization, data is kept in the database and analysed separately and as part of the overall analyses as described in the Statistical Analysis Plan.

LEO owns the data collected in the CRF and as PRO. General Data Protection Regulation (European Commission, 2016) (GDPR) must be adhered to, in addition to any local laws and regulations regarding data privacy. The study must follow the EFPIA HCP Code Article 15 Non-Interventional Studies of Marketed Medicines (The European Federation of Pharmaceutical Industries and Associations, 2008).

The Study Master File compiled by the CRO should be transferred to LEO affiliate when complete. The Complete Study Master File comprises both LEO and CRO compiled documents but should not hold duplicates.

The Study Database compiled by CRO should be transferred to LEO HQ when complete.

Safety data collection and reporting from this NIS must follow the current version of the EMA Guideline on Good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products (European Medicines Agency, 2017). For reporting please refer to Section 11.

The data extracted from medical records and databases is not owned by LEO. The collection must be guided by relevant guidance documents, e.g. Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data (Food and Drug Administration, 2013), the ISPOR Good Research. Practice for Retrospective Database Analysis Task Force Report (Berger et al., 2009), and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology and Code of Conduct (European Medicines Agency, 2010).

When collecting database data, collection and submission of single case safety data is not required. For data collected from medical records, please refer to Section 11.



9.7 Data Analysis

This study is observational and epidemiological methods will be employed for data analyses. Descriptive analysis will be performed of all collected data, except data collected only for the purpose of data cleaning.

Section 9.7.1 describes the statistical analyses as foreseen at the time of planning the study. Any known deviations from the planned analyses, the reason for such deviations and all alternative/additional statistical analyses that may be performed as well as the final statistical analysis must be described in a revised Statistical Analysis Plan (SAP) before completion of data collection. All later deviations and/or alterations will be summarised in the Clinical Study Report.

9.8 Statistical Analysis Plan

Data analyses will be performed using SAS Version 9.4 or further (SAS Institute, Cary, NC USA software).

Quantitative parameters will be described using the following summary descriptive statistics: number of non-missing values, mean, standard deviation, median, first and third quartiles, and minimum and maximum values.

Qualitative parameters will be described overall using frequencies and percentages. Percentages will be calculated on the number of non-missing observations.

The level of significance for all comparisons is set at 0.05 using two-tailed tests. Confidence intervals at 95% could be provided, if relevant.

9.8.1 Description of the population

The safety population will comprise all included patients having received at least one dose of treatment.

The efficacy population will comprise all included patients who fulfill all inclusion and exclusion criteria.

The total number of patients included in the study, in each analysis population and related reasons of exclusion will be described.

The total number of patients attended each visit, number and reasons of study discontinuation will also be described.



9.8.2 Baseline characteristics

Baseline and demographic characteristics will be described on the analysis population and will be summarized using appropriate summary statistics such as mean, standard deviation, median, minimum and maximum for continuous variables, and frequency counts and percentages for categorical variables.

9.8.3 Sensitivity/sensibility analysis

- Analysis of the primary endpoint

The primary endpoint will be the evaluation at week 12/16 of the sensitivity and the specificity, compared to the DLQI as a standard, of the PSO-TARGET QoL component grid to assess the level of satisfaction of patient achieving the therapeutic goal, identified by himself.

The therapeutic objective will be considered as achieved if the patient gives the responses “Satisfied” or “Very Satisfied” on the Likert scale. The response will then be compared to the DLQI score at 12/16 weeks.

It will be described on the efficacy population.

A contingency table will be constructed as follows:

PSO-TARGET \ DLQI	0-1	2-5	6-10	11-20	21-30
Very satisfied	TP	FP	FP	FP	FP
Satisfied	TP	FP	FP	FP	FP
Unsatisfied	FN	TN	TN	TN	TN
Very unsatisfied	FN	TN	TN	TN	TN



This table can be summarized as :

PSO-TARGET \ DLQI	0-1	≥ 2
Very satisfied ou Satisfied	TP	FP
Unsatisfied ou Very unsatisfied	FN	TN

TP: True positive

FP: False Positive

FN: False Negative

TN: True Negative

The validity of the QoL component grid will then be assessed by calculating the following parameters:

Sensitivity: defined as the probability to have patients who have reached their therapeutic target (who have responded « satisfied » or « very satisfied » on the Likert scale, globally and in each major domains) among patients with a DLQI score between 0 and 1.

In other terms the sensitivity is defined as the **concordance** of the QoL component grid and the DLQI **for the patients with optimal quality of life**.

The sensitivity is calculated by:

$$Se = \frac{TP}{TP + FN}$$

Specificity: defined as the probability to have patients who have not reached their therapeutic target (who have responded « unsatisfied » or « very unsatisfied » on the Likert scale, globally and in each major domains) among patients with a DLQI score ≥2.

In other terms the specificity is defined as the **concordance** of the QoL component grid and the DLQI **for the patients with suboptimal quality of life**.

The specificity is calculated by:

$$Sp = \frac{TN}{FP + TN}$$

The QoL component grid will be validated if these two parameters reach the threshold of 85%.



Objective	Statistical analysis	Exposure measure	Outcome measure	Covariables
1	Contingency table; Sensitivity / Specificity	N/A	Concordance level between PSO- TARGET Component grid and DLQI at 12/16 weeks	N/A

- Analysis of the secondary performance endpoints

Analyses of secondary endpoints will be performed on the efficacy population.

No replacement of missing data will be performed.

The same analysis as the primary performance analysis will be performed at 52 weeks.

9.8.4 Efficacy analysis

- Secondary objective/endpoint : achievement of target objective at 12 weeks, per component

Evaluation at week 12/16 of the level of achievement of the main treatment goal identified by the patient in the table at baseline. This evaluation will be performed using a Likert scale in 4 points (“very satisfied”, “satisfied”, “unsatisfied”, “very unsatisfied”).

The achievement of the main treatment goal will be defined as a “satisfied or very satisfied” response.

It will be described on the efficacy population.

- The proportion of patients with achievement of the main treatment goal will be described and the confidence interval at 95% will be provided.
- The primary analysis will be performed with considering missing data as non responder, and a sensitivity analysis will be performed on patients without missing data (observed case).
- Search for predictive factors of efficacy.

The predictive factors of the achievement of the main treatment goal on completed patients will be searched among baseline characteristics using binary logistic regressions models. Univariate analyses will be used to select ($p\text{-value} \leq 0.20$) the explanatory variables to include



in the multivariate model. The results of univariate and multivariate analyses will be interpreted in terms of odds-ratios with their 95% confidence intervals

In case of correlated variables, only the more significant in univariate will be include in the multivariate model.

Variables with a rate of missing data $\geq 20\%$, or those with empty categories or with very small number will not be considered eligible for this research of predictive factors.

As part of one of the secondary objectives, the analyses performed for the efficacy endpoint are summarized in the table below :

Objective	Statistical analysis	Exposure measure	Outcome measure	Covariables
2.a	Proportions	N/A	Achievement of the main goal (yes /no) at 12/16 weeks	N/A
2.b	Proportions – sensitivity analysis	N/A	Achievement of the main goal (yes /no) at 12/16 weeks	N/A
2.c	Binary logistic regression models,	N/A	Achievement of the main goal (yes /no) at 12/16 weeks	Relevant confounders (eg : demographic data, medical history, previous treatment...)
2.d	Proportions	N/A	Achievement of the main goal (yes /no) at 12/16 weeks for each component	N/A

9.8.5 Other secondary analyses

- Description and evolution of PASI

The PASI score will be described at baseline, W12/16 and W52.

The change in the PASI score between baseline and W12/16 then between baseline and W52 will be described by summary descriptive statistics, including 95% confidence interval of the mean.

- Evolution of DLQI

The change in the DLQI score between baseline and W12/16 then between baseline and W52 will be described by summary descriptive statistics, including 95% confidence interval of the mean.



- Level of agreement between the dimensions reported by the patient and by the treating physician.

The proportion of concordant / discordant choices between the dimensions selected at baseline by patient and the physician will be described.

The level of agreement could be evaluated with a Kappa coefficient. Results will be provided in both a quantitative and a qualitative way using the following classes : <0 =« no agreement », [0 ; 0.20]=« slight agreement »,]0.20 ; 0.40]=« fair agreement »,]0.40 ; 0.60]=« moderate agreement »,]0.60 ; 0.80]=« substantial agreement » et]0.80 ; 1]=« almost perfect agreement ».

- Maintenance of target objective at W52

The Maintenance of the main treatment goal will be defined as a “satisfied or very satisfied” response at W52 for patients who have achieved their initial treatment goal at W12/16.

The proportion of patients with maintenance of their main treatment goal at W52 will be described.

- Change of therapeutic objective at the 1st follow-p visit (W12/16).

The proportion of patients who changed their main treatment goal at W12/16 will be described.

- Level of accordance between PASI ≥ 90 and the satisfaction level in regard to the therapeutic objective set by the PSO-TARGET QoL Component grid.
- The change in the PASI score between baseline and the 1st follow-up visit (W 12/16) will be described according to the level of achievement of the main treatment goal (achieved or not). The percentages of patients with a PASI ≥ 90 that responded “satisfied or very satisfied” on the Likert scale at 12 weeks will be calculated and will be compared to the percentages of patients with a PASI ≥ 90 that responded “unsatisfied or very unsatisfied”, using a χ^2 analysis. In case the populations are too small, a Fisher exact test will be used.

The analyses performed for the secondary endpoints are summarized in the table below :

Objective	Statistical analysis	Exposure measure	Outcome measure	Covariables
1	Contingency table; Sensitivity / Specificity	N/A	Concordance level between PSO- TARGET Component grid and DLQI at 12/16 weeks	N/A



Objective	Statistical analysis	Exposure measure	Outcome measure	Covariables
2.a	Proportions	N/A	Achievement of the main goal (yes /no) at 12/16 weeks	N/A
2.b	Proportions – sensitivity analysis	N/A	Achievement of the main goal (yes /no) at 12/16 weeks	N/A
2.c	Binary logistic regression models,	N/A	Achievement of the main goal (yes /no) at 12/16 weeks	Relevant confounders (eg : demographic data, medical history, previous treatment...)
2.d	Proportions	N/A	Achievement of the main goal (yes /no) at 12/16 weeks for each component	N/A
3.a	Means	N/A	Description and evolution of PASI score at 12/16 then 52 ± 4 weeks	N/A
3.b	Mixed effect model with repeated measurement	N/A	Evolution of PASI score over the 52 ± 4 weeks	PASI score at baseline
3.c	Means	N/A	Description and evolution of DLQI score at 12/16 then 52 ± 4 weeks	N/A
3.d	Mixed effect model with repeated measurement	N/A	Evolution of DLQI score over the 52 ± 4 weeks	DLQI score at baseline
3.e	Proportions. Khi-Square analysis	N/A	PASI≥90 versus satisfaction level (QoL Component grid)	
4.a	Proportions	N/A	Proportion of concordant choices (yes /no)	N/A
4.b	Kappa coefficient	N/A	Agreement for the selected dimension between patient and physician	N/A
5.a	Proportions	N/A	Maintenance of the main goal (yes /no) at 52 ± 4 weeks	N/A



Objective	Statistical analysis	Exposure measure	Outcome measure	Covariables
6.a	Proportions	N/A	Change of the therapeutic objective (yes /no) at 12/16 weeks	N/A

9.8.6 Safety analysis

Study AEs will be tabulated in the final report. AEs will be classified by system organ class (SOC), preferred terms (PT) in accordance with the current version of the Medical dictionary for Regulatory Activities (MedDRA), causality and seriousness.

Safety analyses will be performed on the Safety population.

9.9 Quality Control

LEO Pharma and/or its designee will monitor study data to ensure data quality and conformance to Good Clinical Practices (GCPs). Verification of Case Report Form (CRF) data to source documentation, assessment of study progress and assessment of Investigator compliance to study protocol and Ethics Committee/IRB requirements will be performed according to a pre-defined monitoring plan.

9.9.1 Data Collection

Data will be collected on printed CRFs by the investigators. The completed CRFs as well as the completed questionnaires will be sent to the CRO and entered by a data manager into a computer database developed specifically for this study.

Data will remain anonymous.

Access to the database will be restricted to personnel responsible for data entry and to data management and statistics personnel who are directly involved in the management or analysis of this study. Investigators will not have access to the computer database.

9.9.2 Data monitoring

The Monitoring Plan is a separate document, in which detailed monitoring arrangements such monitoring frequency, timing of monitoring visit, access to source data etc. are defined.

The level of source data verification will be set in the Monitoring Plan.



The Clinical Research Associate (CRA) will always refer to the currently valid version of the Monitoring Plan. Monitoring will be performed by outsource consultant according to validated procedures as detailed in the Monitoring Plan.

9.9.3 Data validation

All data management activities will be described in the Data Management Plan.

During the study, data queries will be generated for data items that are potentially erroneous and require appropriate clarification or correction. Prior to database lock, statistical verification of the data will be undertaken in order to further assure data quality.

Over the course of the study, the investigator and the members of the investigator's team agree to be available during regular Quality Control visits by the Clinical Research Associate. During these visits, the following points will be reviewed:

- Signed informed consent;
- quality of the data collected in the CRFs: accuracy, missing data, consistency of the data with the 'source' documents (medical files, appointment books, original copies of laboratory results, etc.).

9.10 Limitations of Research Methods

The complementary value of observational studies relies on their robustness for extrapolation to the background environment that they aim to represent. Thus, the study population shall be representative which means minimization of site selection bias and patient selection bias. In studies of patient treatments, the treatment must be representative, meaning the existence of the study should not impact prescription habits.

However in the current study we are observing Kyntheum® users, the estimates will be affected by selection bias, e.g. Confounding by indication and channelling bias. Those patients the dermatologist chooses to treat with Kyntheum® in the first time after launch, are likely to be the most severe patients who have failed on other treatments available (bias by indication) and those patients that are “channelized” to the study sites and further chosen as study subjects might differ systematically from that group of patients we are trying to describe (channelling bias). The influence of channelling bias is tried minimized by consecutive enrolment, ensuring that patients are not chosen by the investigator to participate in the study. Additionally we expect selection bias due to informed consent, confounding by missing data and attrition depending on disease severity.



Acknowledging that the study is prone to many sources of bias and confounding, the design of this study has been optimized to reflect the patient journeys to the extent possible.

9.11 Other Aspects

Audits and Inspections

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

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

Archiving of Study Data and Documentation

During the course of the study the Site Responsible must as a minimum file the essential documents (Section 3), the protocol (all used versions), the list of participating patients, the written informed consents, the CRFs and the progress reports in the Study Site File. After final database lock the Site Responsible must as a minimum store the list of participating patients and the signed Informed Consent Forms on site for at least 5 years or according to local regulations (if a longer archiving period is required). The Site Responsible should store additional study documentation for a longer period of time as required by any local regulations and/or hospital/clinic requirement.

LEO shall maintain the data and the documentation relating to the study for at least 5 years after the studied product is no longer on the market in any country.

10 Protection of human subjects

This study is a non-interventional study where the existence of the study has no impact on the patient. The treatment of the participating patients will not be any different from patients not participating in the study, except for collection of informed consent to use of the patient's data. Informed consent from the patients shall be collected in order to allow collection of non-standard data such as the psychosocial component and for data monitoring purposes.

The Site Study Responsible must give the patient (and if applicable, legal guardian) oral and written information about the study in a form that the patient (or legal guardian) can



understand, and obtain the patient's (and if applicable, the patient's assent and the legal guardian's) written consent before collection by LEO of identifiable patient information (hereinafter referred to as personal data). The patient (or legal guardian) must agree that his/her data will be processed, stored and may be transferred to third parties, e.g. other companies or authorities, that may be located in other countries with potentially different regulations for data. Additionally the patient (or legal guardian) must agree that his/her data will be transferred to LEO HQ and used for multinational analysis. Before consenting, the patient (and if applicable, legal guardian) must be given sufficient time to consider and to pose questions. Since the study is observational, the consent only concerns the data collection per se and is not consent to any interventional procedure or treatment.

The patient or legal guardian, if applicable, has the right to withdraw his/her consent at any time without prejudice. In the Informed Consent Form it is stated that if consent is withdrawn, any data collected before withdrawal of consent will be kept. The original, signed Informed Consent Forms must be kept on the Site.

Data erroneously collected from patients for which written consent is not available, will not be included in or will be deleted from the database, as feasible.

For details, see the Patient Information Sheet and Informed Consent Form.

This study will be conducted in accordance with the current version of the Declaration of Helsinki (World Medical Association, 2013), The European Federation of Pharmaceutical Industries and Associations (EFPIA) HCP Code, Article 15 Non-interventional Studies of Marketed Medicines (The European Federation of Pharmaceutical Industries and Associations, 2008), Good Pharmacoepidemiology Practices (Public Policy Committee, 2016) and any local regulations. Special attention will be paid to data privacy protection; General Data Protection Regulation (GDPR (European Commission, 2016)), LEO Pharma A/S, Industriparken 55, Ballerup will be the data holder.

LEO/CLINACT will ensure that the protocol and any amendments and the Patient Information Sheet/Informed Consent Form, Diary and Questionnaires are submitted to the relevant Independent Ethics Committees (IECs) and/or competent authorities and/or other national or regional authorities according to local requirements. According to applicable regulations, LEO, CLINACT will submit required documents to the IEC, such as:

- periodic updates on the progress of the study
- notification of the end-of-study
- a summary of the study results



LEO will keep a copy of all documents submitted and an updated list of all submission and approval dates of all documents submitted to the IEC and/or authorities and will provide the Site Responsible with a copy of this list. Copies of the documents will be distributed upon request.

None of the data planned to be collected are expected to have any psychological impact on the participants, and the questions posed will be presented in a non-judgmental, objective manner so that the impact on the patient's behaviour and honesty in data reporting is minimized. The nature of the collected data will not make it possible to track the patients without access to the participant lists and Consent Forms stored at the Study Site. The collection of this data is considered ethically justified, based on these precautions and the following considerations.

This study focuses on collecting data on the real-life experience of biologic treated psoriasis patients for up to 56 weeks.

It will be a challenge to keep patients motivated to contribute data to the study long-term, but psoriasis patients are generally very willing to share their experience with those lending non-judgmental ears to their experience.

The Site Study Responsible must give the patient oral and written information about the study in a form that the patient can understand, and obtain the patient's written consent before collection of identifiable patient information (hereinafter referred to as personal data). Before consenting, the patient must be given sufficient time to consider and to pose questions. Since the study is observational the consent only concerns the data collection per se and is not consent to any interventional procedure or treatment.

The patient must agree that his/her data will be transferred to LEO and processed and stored, and shared with other business partners responsible for Kyntheum® in other markets. In addition, the patient must agree that authorized representatives from LEO or local authorities with inspection rights get access to their consent documentation and medical records for quality checks on protocol compliance and the data entries if requested. Written informed consent to use of collected data must always be obtained before collection of any personal, sensitive data. Data erroneously collected from patients for which written consent is not available, will not be included in or will be deleted from the database, as feasible.

The patient has the right to withdraw his/her consent at any time without prejudice. In the Informed Consent Form it is stated that if consent is withdrawn, any data collected before withdrawal of consent will be kept. The original, signed Informed Consent Forms must be kept on the Site.



11 Management and Reporting of Adverse Events and Other Experiences

11.1 Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Drug Reaction

An Adverse Drug Reaction (ADR) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. ADRs may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure.

Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors

Other Experiences

Other Experiences (OE) are considered 'non events' which describe the circumstances around the use of a drug which potentially could cause drug related problems or which could potentially give positive knowledge of a drug. These may or may not be associated with adverse events.

These events include but are not limited to: unintended beneficial effects, drug exposure in utero, drug exposure via breast milk, drug exposure before and/or during pregnancy, paternal drug exposure before and/or during pregnancy, occupational exposure, drug overdose or abuse, drug misuse, medication error (including potential and intercepted), off label use/unapproved use, lack of efficacy, loss of efficacy, drug and food interaction, any suspicion of counterfeit product, and suspected transmission of an infectious agent by a medicinal product.



Seriousness

A serious ADR or AE is any ADR or AE which results in death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above.

Any suspected transmission of an infectious agent via a medicinal product is considered a serious ADR.

Severity

Severity is a clinical observation and describes the intensity of the event.

- Mild: Transient symptoms, no interference with the patient's daily activities
- Moderate: Marked symptoms, moderate interference with the patient's daily activities
- Severe: Considerable interference with the patient's daily activities.

Causality

- Possible: A reasonable temporal relationship between the medicinal product administration and the event, and there is no other obvious explanation for the occurrence of the event.
- Not related: There is evidence for (an) alternative explanation(s) for the event (e.g. the event is explained by one or more of the following:
 - a) the patient's medical condition,
 - b) a concomitant medication for which the event is labelled, or
 - c) the event occurred prior to the introduction of the medicinal product).

11.2 Physician's responsibility for reporting of Adverse Drug Reactions, Adverse Events and Other Experiences

Physicians and other healthcare professionals involved in the study should report to LEO any AE (including SAEs), OE or pregnancy in patients who are or were treated with Kyntheum[®] within 24 hours of becoming aware of it.



The provided study specific LEO Adverse Event Form – Marketed Products or in case of pregnancies – the Pregnancy Form (Part 1) should be used for the reports and completed carefully, including the section on causality. A copy of the completed form must be sent, within 24 hours, to the Safety Contact Person by email or fax (contact details below).

Contact details of the Safety Contact Persons:**In France:**

Isabelle CHAILLET-VAN MIERLO

Telephone Number: +33 1 30 14 40 25

Email address: pharmacovigilance.fr@leo-pharma.com

fax number: +33 1 30 14 46 13

In Belgium:

Kristien VANELDEREN

Telephone Number: +32 (0)3 740 78 68

Email address: drug.safety.be@leo-pharma.com

The physician should record a precise medical term for the AE or OE, preferably a diagnosis. Please observe that death or surgery are considered as outcome, not as an event, so it is the event leading to death or surgery which should be recorded.

Only one AE or OE should be recorded per form. If no diagnosis is available, the physician should record each sign and symptom on a separate form. For each AE or OE the causality, severity and outcome must be included. Besides the event/experience description, the LEO Study ID, and the subject number in the study should be included.

Important additional information obtained later, e.g. a report of diagnostic procedures or a hospital discharge summary should be incorporated, by the reporter, in a follow-up version of the already reported AE report and a new causality assessment should be made. The follow-up report shall be provided to LEO by the same route as the initial AE report. For non-LEO products, the physician should notify local competent authorities or the concerned manufacturer/ marketing authorization holder, but not both, of AEs at least possibly related to the non-LEO product including a reference to the Study ID or study title.

LEO may request further information from the physician in order to fully assess the safety reports.



11.3 LEO responsibilities for reporting of safety-related data

LEO will notify the Competent Authorities of all serious and non-serious ADRs related to LEO product(s) according to currently applicable pharmacovigilance guidelines for non-interventional studies.

All safety-related data on study patients collected in the study database or reported to LEO according to the normal procedure for marketed drugs, e.g. serious and non-serious ADRs, will be summarized in the Non-Interventional Study Report.

12 Plans for Disseminating and Communicating Study Results

All efficacy and safety data collected in the study will be summarized in the Non-Interventional Study Report

LEO will prepare a Non-Interventional Study Report based on the results obtained. The Final Study Report shall be reviewed and approved by the Coordinating Investigator and be available within one year from collection of the last data point. In case the Coordinating Investigator changes during study conduct, all investigators will be informed and asked for their consent to delegate this responsibility to the new Coordinating Investigator. The sites that have enrolled patients in the study will be informed about the results when the report is finalized. Summary results will be posted on a publicly accessible database.

LEO aims to have the results of this study published, and acknowledges the right of the participating sites to publish results from this study.

A primary publication based on all study data and following the STROBE guidelines (von Elm et al., 2007) in an international peer reviewed journal is foreseen with the Coordinating Investigator as the first or last author, if qualifying as author according to the Vancouver guideline/Good Publication Procedures vs3 (Battisti et al., 2015) with details in reference list. Any manuscripts for secondary publications or abstracts may not be submitted until after the primary publication manuscript has been accepted for publication. Any manuscript or abstract must be sent to LEO for commenting at least 30 calendar days prior to submission.

LEO has the right to use the data and results for regulatory and reimbursement purposes, and for internal presentation within the company and to partners. In addition, LEO may use the data for analysis of pooled data from various studies.



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Annex 1. PSO-TARGET Component Grid

Physical	Subjective	Relational/ social	Therapeutic
Not be limited/handicaped by the pain	Think less or not at all about the disease	Spend quality time with family, friends or colleagues	Need to think less about treatment and care
Do not feel any functional discomfort (itching, rash) in my daily activities	Do not feel any anxiety from the disease	Not caring about what people think about me	Encounter very few, if any, drug discomfort
Have freedom of movement and activities	Feel serene, have peace of mind	Have a fulfilling intimate life	To be cured quickly

