3.0 Abstract

Abstract

Title:

A **C**ross-sectional and retrospective chart review study for assessing pso**R**iasis severit**Y** by absolute PA**S**I score in modera**T**e to severe psoriatic p**A**tients routine**L**y treated with systemic treatment in Bulgaria, Estonia, Hungary, Latvia, Lithuania, Romania and Russia - The **CRYSTAL** Study

Rationale and Background:

Systemic treatment for patients with moderate-to-severe psoriasis includes conventional agents (such as methotrexate, cyclosporine and acitretin), biologics with different modes of action [tumor necrosis factor (TNF) inhibitors, interleukin (IL)-12/23 inhibitors, IL-17 inhibitors], and an oral small-molecule inhibitor of phosphodiesterase-4 (PDE4). However, despite this range of currently available therapies, real-world evidence indicates that a substantial percentage of patients do not achieve skin clearance and are possibly undertreated. At the same time, newer biologic treatment options have raised expectations for treatment success from PASI75 to PASI 90 and even to PASI100. In clinical trial settings, PASI90 and PASI100 response rates with a new class of biologics that targets interleukin (IL)-23 (i.e., IL-23 inhibitors) are high, substantially lowering the percentage of patients with residual disease. Furthermore, several studies show that clear or almost clear skin translates to better HRQoL. In addition to treatment goals of PASI90 and PASI100, absolute PASI $\leq$5, $\leq$3 and $\leq$1 rates are being used in various clinical trials of newer biologics. This concept of 'absolute' PASI is especially useful in routine clinical settings, since baseline PASI is often difficult to obtain. Accumulating evidence suggests that treatment goals defined by absolute PASI targets may enable a more standardized quality of care in the future.

The new classes of biologics (such as the IL-23 inhibitors) recently introduced in routine clinical practice have altered the treatment armamentarium of psoriasis, while additional novel agents within these classes, such as guselkumab, risankizumab, tildrakizumab and mirikizumab, are or will become available in the very near future in Central Eastern Europe (CEE). The absence of nationwide psoriasis patient registries in vast majority of CEE countries, alongside the anticipated introduction of new biologic treatment modalities into the local markets in the near future, highlight the need for real-world evidence studies regarding psoriasis patient clinical management and quality of care. In light of the above, the present study aims to fill this information gap, by characterizing the current state of moderate-to-severe psoriasis patients that have been on systemic treatments for at least 24 weeks, by assessing absolute PASI scores, measuring the burden of the disease in terms of HRQoL, work productivity loss and activity impairment and describing the systemic treatment patterns in the real-world clinical setting in Bulgaria, Estonia, Hungary, Latvia, Lithuania, Romania and Russia.

Research Question and Objectives:

The main research question is:

What is the absolute PASI score and associated HRQoL of moderate to severe psoriatic patients routinely managed with systemic treatment for at least 24 weeks under real-world conditions of daily clinical practice in Bulgaria, Estonia, Hungary, Latvia, Lithuania, Romania and Russia.

Note*: Systemic treatment refers to conventional systemic agents (methotrexate, cyclosporine, acitretin), biologics, and the oral small-molecule inhibitor of PDE4 (apremilast). Photochemotherapy [PUVA] is less and less used in psoriasis in CEE countries and UVB is used only in mild psoriasis or specific patients population like childhood/adolescence*.

Primary Objective:

- To characterize the current disease severity, by assessing the absolute PASI score of patients with moderate to severe psoriasis that have been under continuous systemic treatment (either as monotherapy or as combination regimens) for at least 24 weeks.

Secondary Objectives:

- To assess the absolute PASI ≤1/≤3/≤5 response rates at enrollment, and to capture the duration of the current absolute PASI score, overall and by current systemic treatment option.

  Note: *Systemic treatment option will be examined by type (monotherapy, combination regimen; conventional systemic agents, biologics [TNF inhibitors, IL-12/23 inhibitors, IL-17 inhibitors], oral small-molecule inhibitor of PDE4)*
- To assess the absolute PASI >5 and >8 rates at enrollment, overall and by current systemic treatment option.
- To describe patient treatment history (i.e., all pharmacological and non-pharmacological treatments received from psoriasis diagnosis until enrollment).
- To describe current systemic treatment for psoriasis [i.e., chemical substance(s), starting dosage(s), treatment duration, any dosage intensification(s) that have occurred from the start of the current treatment until enrollment, and dosage at enrollment].
- To describe the demographic and clinical characteristics of patients with moderate to severe psoriasis routinely managed with systemic treatment, in the overall study population.
- To assess both dermatology-specific and generic HRQoL at enrollment, by the use of the DLQI and the EQ-5D-5L questionnaire, overall and by current systemic treatment option.
- To evaluate the correlation of the dermatology-specific and generic HRQoL with the absolute PASI scores of the overall study population at enrollment.
- To assess the psoriasis-related work productivity loss and activity impairment at enrollment through the use of the Work Productivity and Activity Impairment Questionnaire:Psoriasis (WPAI:PSO) questionnaire in the overall study population and in the different groups of patients by current systemic treatment option and by absolute PASI at enrollment (i.e., PASI ≤1, ≤3, ≤5, and >5).
- To assess patient satisfaction with the overall control of psoriasis achieved with the current treatment, as measured at enrollment using a single-item 7-point Likert-type scale, overall and by current systemic treatment option.
- To identify potential patient parameters, treatment and disease characteristics of interest (including concurrent psoriatic arthritis [PsA]), that might be associated with absolute PASI score at enrollment.

Exploratory Objective:

- To assess the absolute PASI score by current systemic treatment option.

Study Design:

This is an epidemiological, multi-country, multicenter, cross-sectional and retrospective chart review study with a single-visit data collection schedule, which will include a representative sample of patients diagnosed with chronic moderate to severe plaque-type psoriasis routinely treated by hospital- and office-based dermatology specialists practicing in geographically diverse locations throughout Central and Eastern European countries.

In line with the purely observational and non-interventional nature of the study, no changes to the current standard of care will be required and all aspects of treatment and clinical management of patients will be in accordance with local clinical practice and applicable national regulations, and at the discretion of the participating physicians.

The study will be completed in a single patient visit which will take place within the normal clinical practice setting, and study-related information will be collected through routine clinical assessments that will be performed at the study visit, patient self-report and self-administered patient-reported outcomes (PROs), as well as through retrospective medical chart review (to the extent available in the medical charts).

The data that will be collected in the cross-sectional part of the study (i.e., at the study visit) include sociodemographic and anthropometric characteristics, current smoking habits and alcohol intake, current disease severity by absolute PASI and clinical characteristics, comorbidities, current treatment for psoriasis, and patient-reported outcomes (in terms of HRQoL, work productivity and activity impairment, and patient satisfaction with treatment), as well as information on current or recent systemic medications prescribed for reasons other than psoriasis, which may impact the clinical assessments and/or the PRO measures. In addition, retrospective data collection will include disease characteristics at psoriasis diagnosis, clinically relevant medical/surgical history, past treatments for psoriasis, and information about the current treatment from its initiation until enrollment [i.e., date of current treatment initiation, starting dosage, and any dosage intensification(s)].

Data collection will take place by means of electronic case report forms incorporated into a project-specific web-based data capture platform that will adhere to all applicable data protection regulations and requirements with regard to electronic records and database validation.

The study will be designed, conducted and reported in accordance with the ethical principles laid down in the Declaration of Helsinki, the Good Pharmacoepidemiology Practices guidelines of the International Society for Pharmacoepidemiology, the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, where applicable, and the local rules and regulations.

Overall, approximately 630 psoriatic patients are planned to be included in the study over a 6-month recruitment period by approximately 50 research sites (hospital clinics and private offices) in Central and Eastern European countries. A sample size of 630 patients produces a two-sided 95% Confidence Interval (CI) with a distance from the mean to the limits that is equal to 0.078 when the estimated standard deviation is 1.0; i.e., the 95% CI will extend up to 0.078 from the observed absolute mean of PASI assuming that the SD is equal to 1.

Participating physicians will be requested to consecutively, thus non-selectively, enroll the first eligible patients (based on the site-specific targets) attending their clinic/office in the context of a routine visit over the study recruitment period.

Patient Selection Criteria

Inclusion Criteria

- Male or female outpatients aged between 18 and 75 years old (inclusive) at the time of informed consent signature.
- Confirmed diagnosis of moderate to severe chronic plaque-type psoriasis diagnosed by a specialist at the time of initiating the current systemic treatment for psoriasis.
- Patients currently treated with any approved systemic treatment for psoriasis, either as monotherapy or combination therapy, continuously for at least 24 weeks.
- Patients with available absolute PASI score at the start of their current systemic treatment, and for whom the study physician plans to assess their absolute PASI score at the study visit as per his/her routine practice.
- Patients able to understand and communicate with the investigator and comply with the requirements of the study.
- Patients must be willing and able to read, understand and complete the provided patient questionnaires.
- Patients must provide written informed consent form (ICF) for collecting and analyzing their medical data pertinent to the objectives of this study.

Exclusion Criteria

- Patients not willing to participate in the study.
- Patients who are currently receiving treatment with any investigational drug/device/intervention or have received any investigational product within 1 month or 5 half-lives of the investigational agent (whichever is longer) prior to enrollment.

Data Analysis:

Statistical analysis will be performed using SAS® statistical analysis software. Categorical variables will be presented as absolute and relative frequencies. For continuous variables, summary statistics will be tabulated. Correlations between continuous variables (i.e., HRQoL and absolute PASI score at enrollment) will be examined using Pearson's or Spearman's correlation coefficient, as applicable. The effect of factors of interest on the primary outcome variable (i.e., absolute PASI score at enrollment) will be assessed by general linear models [i.e. linear regression model, Analysis of Variance (ANOVA), Analysis of Covariance (ANCOVA)] using both the univariable and multivariable approach. All statistical analyses will be performed in the set of all eligible patients with available data. Where indicated by the study objectives, analyses will also be performed in the study subpopulations by current systemic treatment option and by absolute PASI score at enrollment. No imputation methods will be applied with the exception of partial dates. All the aforementioned exploratory statistical tests will be two-sided and will be performed at a 0.05 significance level. No interim analysis is planned to be conducted.