Non-Interventional Study (Non-PMOS)

Protocol

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
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Table of Contents

1.0 Abbreviations

Abbreviation	Explanation
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CD-ROM	Compact Disk - Read Only Memory
CEE	Central & Eastern Europe
CI	Confidence Interval
CRO	Contract Research Organization
CSR	Clinical Study Report
DALY	Disability-Adjusted Life Years
DLQI	Dermatology Quality of Life Index
DMP	Data Management Plan
DVP	Data Validation Plan
eCRF	electronic Case Report/Record Form
EMA	European Medicines Agency
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels
EQ-VAS	EuroQol Visual Analogue Scale
FDA	Food and Drug Administration
FSI	First Subject In
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practices
HCP	Health Care Professional
HRQoL	Health-Related Quality of Life
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IL	Interleukin

IRB	Institutional Review Board
Abbreviation	**Explanation**
LSO	Last Subject Out
MedDRA	Medical Dictionary for Regulatory Activities
PASI	Psoriasis Area Severity Index
pDCF	Paper Data Clarification Form
PDE4	Phosphodiesterase 4
PsA	Psoriatic Arthritis
PT	Preferred Term
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SFEE	Hellenic Association of Pharmaceutical Companies
SOC	System Organ Class
SOP	Standard Operating Procedure
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TNF	Tumor Necrosis Factor
US	United States of America
WBDC	Web Based Data Capture
WHO	World Health Organization
WHOCC	WHO Collaborating Centre for Drug Statistics Methodology
WPAI:PSO	Work Productivity and Activity Impairment Questionnaire:Psoriasis

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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.

4.0 Amendments

None. This is the original protocol.

5.0 Milestones

Major study milestones and their planned dates are as follows:

Start of Data Collection:	Q3 2020
End of Data Collection:	Q1 2021
Final Report of Study Results:	Q3 2021

Note: The aforementioned planned dates are amenable to change based on the actual date of start of data collection (i.e., First Subject In [FSI]).

6.0 Rationale and Background

6.1.1 Background

6.1.1.1 Epidemiology and Burden of Plaque Psoriasis

Psoriasis affects approximately 2-3% of the worldwide population [1,2] and in Europe, the prevalence for psoriasis in most studies varies between 1% and 4%, with higher in the north than in the south (Augustin M; PsoNet pag 25). Psoriasis prevalence varies largely between countries with geographic latitude being one factor, as reports indicate that psoriasis prevalence in Norway is as high as 11.4% [2]. For the CEE countries the available information shows that the prevalence ranges from 3,5 to 4,0% in Hungary, Slovakia and Latvia; from 2,9% to 3,4% in Czech Republic, Romania, Bulgaria, Estonia and Lithuania; from 2,3% and 2,8% in Poland (Augustin M, PsoNet, pag.25 and 56). European countries have been reported to be among those with the highest psoriasis burden. According to the 2013 Global Burden of Disease report, skin diseases conferred 4.7 million disability-adjusted life years (DALYs), ranking as the 18th leading cause of global DALYs and the fourth leading cause of non-fatal burden from 158 disease and injury categories included in the 2013 estimates. About 10% of the burden of skin diseases was attributed to psoriasis [3]. As of today, it does not exist any specific data on Burden of Disease from CEE countries pooled together.

Plaque psoriasis, the most common type of psoriasis, affects 80%–90% of people with psoriasis and is characterized by well-demarcated, symmetric, and erythematous plaques covered with silvery-white scales accompanied by skin pain, itching and burning [4,5]. Psoriasis has been associated with substantial impairment of the patients' health-related quality of life (HRQoL), comparable to that of patients with ischemic heart disease and diabetes [6,7]. Manifestations of psoriasis often extend beyond the skin. Patients with psoriasis show an increased prevalence of comorbid conditions, including psoriatic arthritis (PsA), cardiovascular diseases, obesity, metabolic syndrome, diabetes, malignancies, depression and depressive symptoms [2,5,8,9,10,11,12,13,14]**.** The presence of

comorbidities has been found to be associated with greater work productivity impairments, lower overall HRQoL and worse skin pain [5,15,16]. Moreover, patients with psoriasis involvement of visible and/or sensitive body areas appear to have worse HRQoL versus those without these conditions [5,17].

6.1.1.2 Psoriasis Management

The goal of psoriasis treatment is to manage the troublesome disease symptoms and improve the patients' HRQoL. Approved treatment options include topical agents, phototherapy, and systemic treatment, the latter of which includes conventional agents (methotrexate, cyclosporine and acitretin); biologic agents with different modes of action; and an oral small molecule which inhibits PDE4 (apremilast). Currently approved drug classes of biologics include tumor necrosis factor (TNF)-α inhibitors, an interleukin (IL)-12/IL-23 inhibitor, and IL-17 and IL-23 inhibitors [18,19,20]. Topical therapy (with possible addition of phototherapy) is indicated for patients with mild psoriasis based on the national standard of care , while systemic treatment (with topical therapy and/or phototherapy) is indicated for patients with moderate-to-severe disease or when adequate control of disease cannot be achieved with topical agents. Patients with moderate-to-severe psoriasis are in most cases first initiated on conventional systemic agents, while biologics and the oral small-molecule inhibitor of phosphodiesterase-4 (PDE4) are used for patients who have failed, have a contraindication to, or are intolerant to treatment with conventional agents and/or phototherapy [19,20,21].

- There are some different specificities among participating countries illustrated below.

- In Bulgaria, according to the current treatment algorithm, patients with moderate-to-severe psoriasis are first initiated on phototherapy and conventional systemic therapy (acitretin, ciclosporin or methotrexate) for at least 6 months. Patients who have failed, have a contraindication to, or are intolerant to treatment with

conventional agents and/or phototherapy are eligible to start biologic therapy. First line biologics are Adalimumab, Etanercept, Ustekinumab; 2nd line - IL-17 (Secukinumab, Ixekizumab) and expected IL-23's (Risankizumab, Guselkumab)

- In Hungary mild-to-moderate psoriatic patients (PASI <15 or BSA <10% or DLQI <10) should start with topical therapies and in case no reduction on disease activity observed, they could switch to systemic therapies or phototherapy. For severe patients (PASI >=15 or BSA >= 10% or DLQI >10) systemic immunomodulatory (DMARD), immunosuppressants, retinoids or phototherapy is recommended and in case not adequate disease control is observed at the end of the induction (12-16 weeks) (PASI50 or BSA decrease by 50% AND DLQI decrease at least by 5 points) biologic therapy (anti-TNF, or anti-interleukin therapy) can be started. In Estonia, international guidelines are followed, exception made on biologics initiation. For biologic initiation patients need to have PASI or BSA ≥10, DLQ ≥10, disease duration more than 6 months and resistance to previous systemic treatment for at least 6 months, alternative standard systemic treatment (acitretin, cyclosporine, methotrexate, shortwave UVB and UVA photo chemotherapy) is contraindicated or not tolerated, for psoriasis patients who requires recurrent hospitalizations or have instable, life threatening psoriasis.

  In Latvia for mild psoriasis topical therapy, following for moderate to severe start with conventional systemic therapy options: A-cyclosporin, MTX, Acitretin, photochemotherapy (PUVA). Biologics are initiated for moderate to severe patients (severity index-PASI ≥ 10; skin damage-BSA ≥ 10%) for the treatment of chronic psoriasis, if concomitant systemic treatment with Cyiclosporin or Methotrexatum and phototherapy has been shown to be ineffective ,contraindicated or intolerable.

6.1.1.3 Evolving goals for the treatment of psoriasis

According to the European guidelines for the management of plaque psoriasis [18,19,21] the efficacy of systemic therapy is assessed at the end of the induction phase (i.e., 12-16 weeks depending on the treatment modality) and during the maintenance phase in order to guide further treatment decision making. Both, the patients' extent and severity of psoriasis, as assessed by the Psoriasis Area Severity Index (PASI), and the patients' HRQoL as determined by the Dermatology Life Quality Index (DLQI), are examined. The treatment regimen should be modified if improvement of PASI is <50%. On the other hand, for patients with a PASI 50-75 response, therapy should be modified if the DLQI is >5 but can be continued if the DLQI is ≤5, while for patients with ΔPASI ≥75 treatment may be continued.

Despite a range of therapies for psoriasis, there is an unmet clinical need in terms of achieving and maintaining treatment goals in real-world settings. In the Swiss Dermatology Network for Targeted Therapies registry, therapeutic targets of PASI75 and PASI90 after one year of systemic treatment were reached in only 58% and 36% of patients, respectively [22]. In addition, data from 2646 patients from the Swedish Registry for Systemic Treatment of Psoriasis indicate that 18% of patients receiving systemic treatment had persistent moderate-to-severe psoriasis defined as PASI ≥10 and/or DLQI ≥10 after >12 weeks of treatment [23]. In a chart-review study of 169 bio-naïve patients treated with biologic therapy at six dermatology clinics in the UK, the 12-month PASI75 and PASI90 response rates were 69% and 22%, respectively, among patients remaining on the same biologic therapy for at least 12 months, while it was 34% and 11% among those who discontinued/switched/modified their treatment within the first year [24]. Furthermore, according to published data from the Danish DERMBIO registry, approximately 35% of patients previously exposed to biologics and 50% of bio-naïve patients achieve a PASI90 response in the first year of biologic treatment, while the respective PASI100 response rates are 28% and 38% [25]. Collectively, these studies suggest that a substantial percentage of patients do not achieve skin clearance and may be undertreated.

At the same time, new biologic agents (such as guselkumab and risankizumab) have raised expectations for treatment success from PASI75 to PASI 90 and even to PASI100 [26,27,28,29,30]. Among them, risankizumab, an IL-23 inhibitor, which was recently granted approval in Japan and in the United States by the Food and Drug Administration and Puerto Rico, Canada, Switzerland, EU/EMA, has demonstrated 1-year PASI90 response rates of about 80%, and PASI100 rates of 55-60%, substantially lowering the percentage of patients with residual disease [29,30].

In addition to treatment goals of PASI90 and PASI100, absolute PASI ≤5, ≤3 and ≤1 rates have been used in various clinical trials of newer biologics [26]. Moreover, absolute PASI is also included in the decision algorithm for psoriasis treatment of the Spanish and Italian guidelines [31,32]. This concept of ‘absolute’ PASI is especially useful in routine clinical settings, since baseline PASI is often not at hand. Absolute PASI offers several advantages

over relative PASI. First, absolute PASI is independent of the baseline value, it is particularly valuable when measuring efficacy beyond 24 weeks of treatment, after which time baseline PASI is not expected to be of much relevance [26]. Achievement of a PASI score lower than 2 or 3, is an indication of treatment success, while a score greater than 5 indicates that an alteration of treatment is needed, independent of the baseline PASI score [33]. In addition, a PASI90 response is more difficult to be achieved among patients with a low, than in those with a high, baseline PASI score. In the BioCaPTURE real-world registry a PASI≤5 response was achieved by 52% of patients that did not attain a PASI90 and by 58% of those that did not attain a PASI100 [34]. The evidence suggests that treatment goals defined by absolute PASI targets may enable a more standardized quality of care in the future.

Furthermore, several studies indicate that clear or almost clear skin translates to better HRQoL and is a clinically meaningful target [35,36]. The correlation of PASI with HRQoL, examined using the DLQI, but also the EuroQol five-dimensions (EQ-5D) visual analogue scale (VAS) score and utility index score has been documented [37,38,39,40]. Interestingly, the correlation between DLQI and PASI appears to be stronger among patients receiving biologics [41]. Moreover, in patients with moderate-to-severe plaque psoriasis, higher absolute PASI scores have been associated with reduced HRQoL, but also with greater work productivity impairment [42]. Furthermore, patient satisfaction with treatment also seems to be an important factor to consider when striving for better patient outcomes, as it has been associated with better HRQoL [42,43], but also lower disease severity [43].

6.1.2 Rationale

New drug classes of biologics (such as the IL-17 and IL-23 inhibitors) for the treatment of psoriasis have recently been introduced in routine clinical practice thus altering the treatment armamentarium of psoriasis, while additional novel agents within these classes, such as risankizumab, are expected to become available in the very near future in Central and Eastern European countries.

The absence of nationwide psoriasis patient registries, alongside the expected introduction of new biologic treatment modalities of psoriasis 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 treatment 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 real-world systemic treatment patterns in real-world clinical settings in Bulgaria, Estonia, Hungary, Latvia, Lithuania, Romania and Russia.

7.0 Research Question, Objectives and Endpoints

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.

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 adolescence.

The study is descriptive in nature and is not planned to reject or affirm any formal statistical hypothesis. The study objectives are described below in Sections 7.1 and 7.2. The primary and secondary outcome measures/endpoints that will be accounted for in order to address these objectives are thoroughly presented in Sections 7.1.1 and 7.2.1 and the relevant variables in Section 9.4.

7.1 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.

7.1.1 Primary Endpoint

- Mean absolute PASI score of the overall study population at enrollment.

7.2 Secondary Objectives

1. 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)*

2. To assess the absolute PASI >5 and >8 rates at enrollment, overall and by current systemic treatment option.

3. To describe patient treatment history (i.e., all pharmacological and non-pharmacological treatments received from psoriasis diagnosis until enrollment).

4. 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].

5. To describe the demographic and clinical characteristics, of patients with moderate to severe psoriasis routinely managed with systemic treatment, in the overall study population.

6. 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.

7. To evaluate the correlation of the dermatology-specific and generic HRQoL with the absolute PASI scores of the overall study population at enrollment.

8. 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).

9. To assess patient satisfaction with the overall control of psoriasis achieved with the current systemic treatment, as measured at enrollment using a single-item 7-point Likert-type scale (anchored by "completely dissatisfied" and "completely satisfied"), overall and by current systemic treatment option.

10. To identify potential patient parameters, treatment and disease characteristics of interest (including concurrent PsA) that might be associated with absolute PASI score at enrollment.

7.2.1 Secondary Endpoints

- Proportions of patients with absolute PASI score ≤1, ≤3, and ≤5 at enrollment, overall and by current systemic treatment option *(corresponding to secondary objective#1).*

- Physician-reported duration of the current absolute PASI score, 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 and ≤5) *(corresponding to secondary objective#1).*

- Proportions of patients with absolute PASI score >5 and >8 at enrollment, overall and by current systemic treatment option *(corresponding to secondary objective#2).*

- Patient treatment history *(pharmacological and non-pharmacological; topical therapy/systemic therapy/phototherapy)*, systemic treatment type *(conventional systemic agents at a chemical substance level, biologics at a drug class level [TNF inhibitors, IL-12/23 inhibitors, IL-17 inhibitors], oral small-molecule inhibitor of PDE4)* used for psoriasis management since disease diagnosis *(corresponding to secondary objective#3).*

- Current systemic treatment by type *(monotherapy, combination regimen; conventional systemic agents, biologics [e.g. TNF inhibitors, IL-12/23 inhibitors, IL-17 inhibitors], oral small-molecules, e.g. inhibitor of PDE4)* and chemical substance, treatment duration, starting and current dosage and dosage intensification(s) since

current treatment initiation, including reasons for intensification(s) *(corresponding to secondary objective#4).*

- Summary descriptive statistics of demographic and clinical characteristics of interest of patients routinely managed with systemic treatment, in the overall study population (the characteristics to be collected and summarized are described in detail in Section 9.4) *(corresponding to secondary objective#5)*.

- Summary statistics of DLQI total and domain scores at enrollment, overall and by current systemic treatment option *(corresponding to secondary objective#6)*.

- Proportion of patients with DLQI total score 0-1 *(i.e., no effect at all of skin disease on patients' HRQoL)*, 2-5 *(i.e., small effect of their skin problem on patients' HRQoL)*, and >5 *(i.e., at least a moderate effect on patients' HRQoL)* at enrollment, overall and by current systemic treatment option *(corresponding to secondary objective#6)*.

- Summary statistics of EQ-5D-5L utility index score and EQ-VAS score at enrollment, overall and by current systemic treatment option *(corresponding to secondary objective#6)*.

- Proportion of patients with reported problems for each level on each dimension of the EQ-5D and proportion of patients with 'no problems' (i.e., level 1) and 'with problems' (i.e., level 2 to 5) at enrollment, overall and by current systemic treatment option *(corresponding to secondary objective#6)*.

- Correlation coefficient between the absolute PASI score and the DLQI total score of the overall study population at enrollment *(corresponding to secondary objective#7)*.

- Correlation coefficient between the absolute PASI score and the EQ-5D utility index of the overall study population at enrollment *(corresponding to secondary objective#7)*.

- Correlation coefficient between absolute PASI score and EQ-VAS score of the overall study population at enrollment *(corresponding to secondary objective#7)*.

- Mean WPAI:PSO domain scores referring to absenteeism, presenteeism, work productivity loss and activity impairment, 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) *(corresponding to secondary objective#8).*

- Proportions of patients per satisfaction level as well as of those who are satisfied with the control of their psoriasis with the current treatment *(i.e., who scored the Likert scale as somewhat satisfied, mostly satisfied or completely satisfied)* at enrollment, overall and by current systemic treatment option *(corresponding to secondary objective#9)*.

- Association of current treatment, disease duration, disease severity (absolute PASI score) at current treatment initiation, previous treatment(s), patient characteristics, concurrent PsA, and comorbidities with the absolute PASI at enrolment (the parameters of interest are described in detail in Section 9.5) *(corresponding to secondary objective#10)*.

7.3 Exploratory Objective

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

7.3.1 Exploratory Endpoint

- Mean absolute PASI score at enrollment by current systemic treatment option.

8.0 Research Methods

8.1 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 Europe.

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 clinical characteristics and psoriasis severity assessed by absolute PASI score, 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 (eCRFs) incorporated into a project-specific web-based data capture (WBDC) 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 (GPP) 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.

This study design has been selected on the basis that such studies essentially, through collecting data about real-world management practices and their outcomes help to bridge the knowledge gap between clinical research which is conducted in strictly controlled randomized settings and that conducted in daily clinical practice. Moreover, as these studies follow less restrictive methodological standards than controlled trials in terms of patient selection, treatment and other design aspects, their results are better generalizable especially for populations with diseases of complex and heterogeneous biology, such as psoriasis. In addition, the cross-sectional aspect of such studies provides a snapshot-based approach to document outcomes of interest and the characteristics associated with these for subgroups of population at a given timepoint in a routine clinical practice setting, which can be used on the planning of health services or the determination of healthcare practices, while being less resource-demanding and less time-consuming compared to other study designs.

Nevertheless, this design also bears several limitations which are thoroughly discussed in Section 9.11.

8.1.1 Visit Schedule and Assessments

In keeping with its non-interventional and cross-sectional nature, this study does not impose any diagnostic/therapeutic interventions or a visit schedule. Patients will be treated and assessed according to the routine medical practice and only these data will be collected as

part of the study. The participating physician will be asked to complete the eCRF as appropriate at the single study visit.

Upon the enrollment of each patient into the study, the participating physician shall follow the below-mentioned procedures:

- Review of patient's medical history and current treatment, in order to confirm if eligibility criteria are met.
- Explanation of the study purpose to the patient and obtainment of signed and dated written informed consent form (ICF), after having provided the required time to the patient to carefully read and understand the patient information leaflet.
- Collection of the data through routine clinical assessments, medical chart review, patient self-report and self-administered PROs, and completion of the eCRF.

The data collection schedule is presented below in Data Collection Schedule.

Data Collection Schedule

Data Collection	Enrollment/ Study Visit
Screening/Patient information	
Selection (eligibility) criteria	X
Patient Informed Consent obtainment	X
Sociodemographic characteristics	X
Anthropometric characteristics	X
Current smoking habits and alcohol intake	X
Current clinical characteristics and psoriasis severity assessed by absolute PASI score	X
Information on current pharmacological and non-pharmacological treatment for psoriasis	X
Information on current or recent use of systemic medications for reasons other than psoriasis, which may impact the clinical assessments and/or the PRO measures	X
Retrospective data from medical chart review	
Information on psoriasis-related history (including PsA)	X
Pharmacological and non-pharmacological treatments prior to the onset of current systemic treatment	X
Clinically relevant medical and surgery history	X
Disease characteristics at psoriasis diagnosis	X
Patient-reported outcomes	
DLQI (completed by the patient at the study visit)	X
EQ-5D-5L (completed by the patient at the study visit)	X
WPAI:PSO (completed by the patient at the study visit)	X
Single-item Likert-type scale for the assessment of patient satisfaction with overall control of the psoriasis with the current treatment (completed by the patient at the study visit)	X

8.2 Study Time Period

The overall study duration is expected to be 6 months, starting *[defined as FSI]* in Q3 2020 and ending *[defined as 'Last Subject Out' (LSO)]* in Q1 2021, or when the full accrual has been achieved (i.e., the overall target sample size has been reached) whichever comes first. In case that the required sample size has not been enrolled until the completion of the planned recruitment period, an accrual time extension may be considered.

The planned study milestones have been presented in Section 5.0.

9.0 Setting

9.1 Researcher Selection

Patients will be enrolled by approximately 50 hospital centers/clinics (in the public or private sector) and private offices in Bulgaria, Estonia, Hungary, Latvia, Lithuania, Romania and Russia specialized in dermatology. The research sites will be medical centers experienced in the treatment of psoriasis. Researchers will have access to psoriasis patient population and have the ability to appropriately conduct the study in accordance with applicable legal and regulatory requirements.

Based on preliminary feasibility projections, it is anticipated that each participating site will recruit a sample of approximately 10-25 patients; nevertheless, it is noted that the sample size per site represents a rough approximation since the study recruitment approach may become competitive in nature among sites/countries in case of low recruitment signals. In addition, the total number of sites to be finally enrolled into the study may change depending on the interest in participation and the volume of potentially eligible patients that each site can contribute to the study. In case the targeted number of active participants cannot be reached, site sample and/or the maximum number of patients per site may be extended and/or enrollment period may be prolonged, depending on the progress of the study.

The type of healthcare site (e.g., office-based physician, publicly or privately owned hospital/institution, university clinic etc.) and the regional setting *(urban/semi-urban, rural)* will be documented for each participating site.

Candidate researchers will originate from a pool of specialists in dermatology across Central and Eastern European countries. The sampling frame will employ a non-probability technique; thus, physicians will be selected in a non-random manner based on specific predefined-criteria. In particular, investigators must be qualified by experience and ability to perform the study and will be finally selected through a documented and constructed feasibility assessment process that will account, among others, for physicians' qualifications, previous participation and experience in similar clinical studies, number of potentially eligible patients, geographic representativeness based on proportionality to the total country population, representativeness in terms of psoriatic cases encountered in routine practice settings, as well as ability to meet protocol requirements and study milestones.

9.2 Patient Selection Criteria

A total of approximately 630 patients are planned to be enrolled over the 6-month study recruitment period. Patient selection will be based on systematic sampling technique, i.e., all consecutive eligible patients are expected to be included in the study. In particular, in order to mitigate confounding due to the potential of patient selection bias, physicians will be requested to consecutively enroll and document the first patients (based on the site-specific target) attending their clinic over the pre-specified study recruitment period that meet the study specific eligibility criteria defined in Sections 9.2.1 and 9.2.2.

A screening log of all potentially eligible patients, i.e., of patients who meet study selection (eligibility) criteria regardless of whether they agree to participate or not, including the minimum required information [i.e., date seen, gender, age range (18-20 years, 21-30 years, 31-40 years, 41-65, and 66-75 on the date seen) and reason for non-consenting (i.e., not interested, language barriers in informed consenting, other)] will be kept at site, to assess potential selective enrollment of subjects.

Patients attending a routine visit who fulfill the following selection criteria *(i.e., who meet **ALL** the inclusion criteria and **NONE** of the exclusion criteria presented below in Sections 9.2.1 and 9.2.2)* can be enrolled.

9.2.1 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.

  Note: Continuous systemic treatment for psoriasis is defined as any systemic therapy *[i.e., conventional systemic agents (methotrexate, cyclosporine, acitretin), biologics (e.g. TNF inhibitors, IL-12/23 inhibitors, IL-17 inhibitors), oral small-molecules, e.g. inhibitor of PDE4 (apremilast)]* that is received by the patient, either as monotherapy or combination therapy, continuously for at least 24 weeks prior to enrollment, without interruptions and changes in at least one of the treatment components, regardless of any dosage adjustments/modifications.

- 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.

  Note: If the absolute PASI score is not available at the start of the current systemic treatment, an absolute PASI sore that has been assessed between 30 days prior and 7 days after the start of treatment is sufficient to satisfy this criterion.

- 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.

9.2.2 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.

9.3 Patient Withdrawal and Replacement

A patient will be withdrawn from data collection within the study for any of the following reasons:

- Patient's withdrawal of informed consent; patients reserve the right to withdraw their consent for data collection at any time and for any reason without having to justify their decision and with no impact on their future medical care and therapy.
- Erroneous enrollment, i.e., the patient does not meet the eligibility criteria for participation in the study.

Furthermore, the participating physicians will have the right to withdraw any patient from the study, if according to their clinical judgment this decision is considered to be in the patient's best interest. In addition, AbbVie reserves the right to discontinue the study overall or at a particular study site at any time (refer to section 9.12.8).

When a patient withdraws from data collection within the study, the reason for withdrawal should be documented in the eCRF, and no replacements will be made after the completion of the study recruitment period.

9.4 Variables

9.4.1 Primary and Secondary Outcome Variables

In the context of this study that involves the collection of both primary data *(that will be collected through clinical assessments performed at the study visit, patient self-report and PROs)* and secondary data *(that has already been obtained as per standard/routine clinical practice and will be retrospectively collected to the extent available from patients' medical records)*- the following variables will be collected in order to address the study objectives.

- Date of enrollment/study visit
- Date of informed consent

Sociodemographic and anthropometric characteristics(cross-sectional part)

- Sociodemographic characteristics
  - Patient age at enrollment *(derived variable from date of birth and date of psoriasis signs and symptoms onset)*
  - Gender (male, female)
  - Race (White, Black, Asian, not reported/unknown)
  - Place of residence (urban, semi-urban, rural, not reported/unknown) at enrollment
  - Health insurance coverage (public, private, public-private mix, no insurance) at enrollment
  - Family/marital status (married, single, divorced/separated, widowed, not reported/unknown) at enrollment
  - Education level (no education, 1-6 years, 7-9 years, 10-12 years, ≥13 years of education, not reported/unknown)
  - Employment status (unemployed, employed, retired, household duties, student, other, not reported/unknown) at enrollment

- Anthropometric characteristics
  - Body weight (kg) at enrollment and at the start of current treatment
  - Height (cm)
  - Body Mass Index (BMI) (kg/m^2) at enrollment and at the start of current treatment *(derived variable that will be automatically calculated in the eCRF based on the recorded weight and height, where available in medical chart-retrospective part)*

Smoking habits and alcohol intake(cross-sectional part)

- Smoking status (conventional cigarette use) at enrollment and lifetime tobacco exposure (never smoker, former smoker, current smoker); if 'former' or 'current' smoker: smoking pack-years, and if 'former' smoker: years since quitting smoking
- Electronic nicotine-containing cigarette vaping and use of heated tobacco products (yes, no); if 'yes', duration of use
- Alcohol consumption over the past month prior to enrollment (no, occasional [i.e., 1-2 units/week], regular, unknown/not reported); if "regular alcohol intake", average number of units of alcohol consumed per week

Disease & clinical characteristics

- Patient age at psoriasis signs and symptoms onset *(derived variable from date of birth and date of psoriasis signs and symptoms onset)* ***(retrospective part from medical chart review)***
- Patient age at psoriasis diagnosis *(derived variable from date of birth and date of psoriasis diagnosis)* ***(retrospective part from medical chart review)***
- Psoriasis duration at enrollment *(derived variable from date of psoriasis diagnosis and date of enrollment)* ***(retrospective part from medical chart review)***
- Psoriasis duration at the start of current treatment onset *(derived variable from date of psoriasis diagnosis and date of current treatment initiation)* ***(retrospective part from medical chart review)***

- Patient age at the start of the current systemic treatment *(derived variable from date of birth and date of current systemic treatment initiation)* ***(retrospective part from medical chart review)***
- Physician-assessed psoriasis severity at initial diagnosis and at the start of the current systemic treatment (mild, moderate, severe, unknown) ***(retrospective part from medical chart review)***
- Absolute PASI score at disease diagnosis ***(retrospective part from medical chart review)***
- Absolute PASI score at the start of the current systemic treatment; if the score is not available at this timepoint, the closest PASI between 30 days prior and 7 days after the start of treatment will be recorded ***(retrospective part from medical chart review)***
- Absolute PASI score at enrollment *(PASI score will be automatically calculated in the eCRF based on the component body area scores)* ***(cross-sectional part)***
- Absolute PASI score at enrollment categorized as ≤1, ≤3, ≤5, >5 but ≤10, >10 but ≤20, and >20 ***(cross-sectional part)***
- Physician-reported duration of the current absolute PASI score ***(retrospective part from medical chart review)***
- Positive family history of psoriasis (yes, no, unknown) ***(retrospective part from medical chart review)***
- History of PsA (yes, no, unknown); if 'yes', date of arthritis symptoms onset, and whether the patient has active PsA at enrollment and at the start of current treatment ***(retrospective part from medical chart review & cross-sectional)***
- Presence of spondylitis, enthesitis, and dactylitis at enrollment and at the start of current treatment (yes, no, unknown) ***(retrospective part from medical chart review & cross-sectional)***

  Presence of nail psoriasis at enrollment and at the start of current treatment (yes, no) (defined as the presence of any kind of change due to psoriasis on at least one nail of a

finger or toe); if 'yes', presence of psoriatic onychodystrophy or onycholysis on at least 2 nails at enrollment and at the start of current treatment (yes, no) ***(retrospective part from medical chart review & cross-sectional)***

- Localization of psoriatic lesions at enrollment (***cross-sectional part)***
- Presence of psoriasis in difficult-to-treat areas (i.e., scalp, face, nails, genitals, and palms/soles) at enrollment (yes, no) (***cross-sectional part)***
- Severe itching/pruritus at enrollment and at the start of current treatment (yes, no) ***(retrospective part from medical chart review & cross-sectional)***

Clinically relevant medical and surgical history/comorbidities (retrospective part from medical chart review & cross-sectional)

- Presence of clinically relevant medical and surgical history/comorbid conditions (yes, no); if 'yes', description of condition, timing of occurrence/diagnosis in relation to the start of the current systemic treatment for psoriasis, and whether it is past or ongoing at enrollment

Current and past treatments for psoriasis (retrospective part from medical chart review & cross-sectional)

- Current pharmacological and non-pharmacological treatment for psoriasis
  - Current systemic therapy → type *[monotherapy, combination treatment; conventional systemic agent, biologic agent (e.g. TNF inhibitors, IL-12/23 inhibitors, IL-17 inhibitors), oral small-molecules, e.g. inhibitor of PDE4]* and chemical substance
  - Date of initiation of current systemic treatment *(in case of combination therapy, the date of initiation of each separate treatment component will be recorded)*
  - Dosage intensification(s) of current systemic treatment since treatment onset (yes, no); if 'yes' description of and reason for dosage intensification(s)
  - Use of topical treatment and/or photo(chemo)therapy for psoriasis since the start of current systemic therapy (yes, no); if 'yes' type of treatment [topical *(corticosteroids; vitamin D analogue, tar-based preparation, retinoid, dithranol,*

calcineurin inhibitors, emollients containing keratolytic agents such as salicylic acid, other), phototherapy, photochemotherapy] and whether it is discontinued or ongoing at enrollment; if 'discontinued', timing of discontinuation (≤ 7 or >7 days prior to enrollment) will be recorded

- Previous pharmacological and non-pharmacological treatments for psoriasis since psoriasis diagnosis
  - Use of topical treatment at any time during the period elapsed between psoriasis diagnosis and the start of the current systemic treatment (which had been discontinued at the start of the current systemic treatment) (yes, no); if 'yes' type of treatment *(corticosteroids; vitamin D analogue, tar-based preparation, retinoid, dithranol, calcineurin inhibitors, emollients containing keratolytic agents such as salicylic acid, other)*
  - Use of photo(chemo)therapy at any time during the period elapsed between psoriasis diagnosis and the start of the current systemic treatment (which had been discontinued at the start of the current systemic treatment) (yes, no)
  - Use of systemic treatment at any time during the period elapsed between psoriasis diagnosis and the start of the current systemic treatment (which had been discontinued at the start of the current systemic treatment) (yes, no); if 'yes' chemical substance(s) will be recorded; as well as the number of previous courses per chemical substance will be recorded for biologic agents only

    Note: A treatment course of biologic agent is defined as a period of time in which the patient received a biologic without interrupting treatment for >90 days; the 90-day interruption period is widely accepted for biologic therapy in psoriasis [44,45,46]

Patient-reported outcomes (cross-sectional part)

- Patient-rated DLQI total score at enrollment *(DLQI total score will be automatically calculated in the eCRF based on the domain scores)*
- Patient-rated individual DLQI domain scores at enrollment

- Patient-rated DLQI total score at enrollment categorized as 0-1, 2-5, >5 but ≤10, >10 but ≤20, and >20
- Level of problems on each dimension of EQ-5D at enrollment, and classification based on the absence or presence of problems [i.e., 'no problems' (level 1) and 'with problems' (levels 2 to 5)]
- Patient-rated EQ-VAS score at enrollment
- EQ-5D-5L utility index score at enrollment *(calculated by the Sponsor designated Statistical Department)*
- Patient-reported WPAI:PSO scores of the absenteeism, presenteeism and overall work impairment (absenteeism plus presenteeism) domains in the study population who is currently employed at enrollment
- Patient-reported WPAI:PSO score of the activity impairment domain in the overall study population at enrollment
- Patient-reported score in regards to his/her satisfaction with the control of his/her psoriasis with the current treatment
- Categorization of the satisfaction level as dissatisfied (scores 1-3), neutral (score 4) and satisfied (scores 5-7)

Current or recent use of systemic medications for reasons other than psoriasis, which may impact the clinical assessments and/or the PRO measures (cross-sectional part)

- Use of systemic medications for reasons other than psoriasis that have been taken within the 30-day period prior to enrollment *[including, among others, corticosteroids, anti-inflammatory agents, analgesics, antibiotics, antidepressants, anxiolytics, and mood stabilizers (either over the counter or through prescription)]* (yes, no); if 'yes', therapeutic class will be recorded, as well as if 'ongoing' or 'discontinued' at enrollment, and if 'discontinued' whether they have been discontinued >7 or ≤7 days prior to enrollment.

9.5 Covariates

The following variables will be considered as covariates and will be examined in terms of their association with the absolute PASI at enrollment:

- Current treatment
- Duration of current treatment
- Disease duration at the start of current treatment
- Prior use of biologic agent(s) before the start of current systemic treatment (biologic-naïve versus biologic experienced)
- Number of previous treatment courses with biologic agents
- Positive family history of psoriasis
- Comorbid PsA, spondylitis, enthesitis, and dactylitis, at the start of current therapy (yes, no)
- Presence of nail psoriasis at the start of current treatment (yes, no)
- Absolute PASI at the start of current treatment (or most recent assessment)
- Patient age at the start of current treatment
- Gender
- BMI at the start of current treatment
- Comorbidities at the start of current treatment

9.6 Data Sources

The study will mainly involve primary data collection, by means of a WBDC system as described in Section 9.8. Data will be collected directly by the participating physicians as generated within the framework of standard clinical practice, through routine assessments that will be performed in the context of the single study visit as well as by the patients as captured with the use of PROs and through self-report (where applicable). No further clinical, laboratory and imaging assessments are required apart from those performed as per the treating physician's routine medical practice.

Patient source data pertaining to medical- and psoriasis-related history, and current and past disease management practices will be abstracted from patients' medicals records and patient self-report, where applicable, and will be recorded in the relevant section of the eCRF. Source documentation should be available in patients' medical records for all data entered into the eCRF except for specific data [i.e., demographics (race, marital status, education level, employment status, place of residence, health insurance coverage), history of smoking and alcohol use] for which the eCRF will serve as the source document, and the patient-completed questionnaires (as described in Section 9.6.2) for which the paper forms will be considered source data.

The physician-assessed disease activity/severity measure (i.e., PASI) is described in the following Section 9.6.1. Furthermore, the PROs described in the following Section 9.6.2 will be collected via self-administered paper questionnaires completed by the patients themselves at study enrollment.

9.6.1 Physician Assessment for Disease Severity and Activity

- **Psoriasis Area and Severity Index (PASI)**

PASI is among the most widely utilized tools and the current gold standard for the assessment of psoriasis [47]. PASI combines the assessment of the severity of lesions and the area affected yielding a single score that ranges from 0 (no disease) to 72 (maximal disease), i.e., higher scores indicate more severe or more extensive psoriasis. It is a measure of the average redness, thickness, and scaliness of the lesions (each graded on a 0–4 scale), weighted by the area of involvement (ranging from 0 to 6) in each of four regions (head and neck; upper extremities; trunk; and lower extremities) of the affected subject [48]. While the PASI has been the most commonly used outcome measure, it bears several limitations, one of which is its poor sensitivity to change for relatively small areas of involvement and its inherent subjectivity resulting in inter-rater and even intra-rater variability [49,50]. Albeit its drawbacks, it is the most adequate instrument available to evaluate severity in plaque-type psoriasis [51].

9.6.2 Patient-Reported Outcomes (PROs)

The following PRO questionnaires/scales will be used in order to capture patient-perceived QoL, work productivity and activity impairment and satisfaction with treatment:

- **Dermatology Life Quality Index (DLQI)**

  The appropriate local language version of the DLQI [52,53] will be used in each country to measure the patient-perceived importance of PsO burden as measured by the impact of psoriasis on the dermatology-specific HRQoL. DLQI is one of the most widely used dermatology-specific quality of life instruments and it has well-established properties of reliability and validity in the dermatology setting [54,55,56,57]; in addition, it has high repeatability, internal consistency, and sensitivity/responsiveness to change [55]. Although it is a specialty-specific rather than disease specific instrument which has been used in over 40 different skin conditions [58], psoriasis is among the indications in which this instruments has been most widely used; in addition its psychometric properties in psoriasis have been well-established [56]. It consists of a set of 10 items/questions concerning the impact of skin disease on different aspects of quality of life over the last week and it is summarized in six sections (symptoms and feelings, daily activities, leisure, work and school, personal relationships, treatment). Each item is scored on a 4-point scale: not at all/not relevant, a little, a lot and very much. Item scores (0-3) are added to give a total score (0-30); higher scores indicate greater impairment of HRQoL. The bands of the DLQI total score are 0-1 (i.e., no effect at all on patients' life), 2-5 (i.e., small effect on patients' life), 6-10 (moderate effect on patients' life), 11-20 (very large effect on patients' life), and 21-30 (extremely large fact on patients' life) [58]. It is self-administered with a mean completion time of 2 min [59]. A sample of the English version of DLQI instrument is presented in Section 15.1 (Appendices).

- **EuroQol 5-Dimension 5-Level questionnaire (EQ-5D-5L)**

  The appropriate local validated language version of EuroQol 5-Dimension 5-Level questionnaire (EQ-5D-5L) will be used in each country in order to measure patient's

multidimensional HRQoL at enrollment. The EQ-5D was developed by the EuroQol Group as a simple, generic measure of HRQoL for clinical and economic appraisal and has been widely used in both general and specific disease populations. EQ-5D is designed for self-completion by respondents and is ideally suited for use in clinics, and in face-to-face interviews. It is cognitively not demanding, taking only a few minutes to complete. The original version of EQ-5D has 3 levels (EQ-5D-3L) and was introduced in 1990 and it essentially consists of the EQ-5D descriptive system and the EQ-VAS. The EuroQol Group has recently introduced the 5-level EQ-5D (EQ-5D-5L), which expands the range of responses in each dimension from three to five levels aiming to improve the instrument's sensitivity, increase reliability, and to reduce ceiling effects [60,61]**.** The EQ-5D-5L descriptive system comprises the following 5 dimensions: *mobility*, *self-care*, *usual activities*, *pain/discomfort* and *anxiety/depression*. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. It should be noted that the numerals 1-5 have no arithmetic properties and are not used as a cardinal score. The EQ-VAS records the respondent's self-rated health on a 20-cm vertical, visual analogue scale where the endpoints are labelled '*the best health you can imagine*' and '*the worst health you can imagine*' and with higher scores indicating higher HRQoL. This information can be used as a quantitative measure of health outcome as judged by the individual respondents. EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, may be converted into a single index value. The index values, presented in country specific value sets, are a major feature of the EQ-5D instrument, facilitating the calculation of quality-adjusted life years (QALYs) that are used to inform economic evaluations of health care [62]. Overall, the validity and responsiveness of the EQ-5D was found to be good in people with skin diseases, especially plaque psoriasis or PsA [63]. A sample of the English version of EQ-5D-5L instrument is presented in Section 15.1.2 (Appendices).

- **Work Productivity and Activity Impairment: Psoriasis (WPAI:PSO) Questionnaire**

Productivity at work and activity impairment will be evaluated in each country using the appropriate local language version of the Work Productivity and Activity Impairment:Psoriasis (WPAI:PSO v2.0) questionnaire which is either self- or interviewer-administered [64]. The WPAI is available in the public domain, and is a quantitative, self-reported evaluation of the level of absenteeism, presenteeism, and daily activity impairment attributable to either disease-related or general health during the prior 7 days [65]. It takes 2 to 3 minutes to complete [66] and comprises six questions that capture the following information:

1. *Employment status;*
2. *Hours of work missed due to problems associated with psoriasis;*
3. *Hours missed because of other reasons;*
4. *Hours actually worked;*
5. *The degree to which psoriasis has affected productivity while working from 0 (no effect) to 10 (maximum impairment); and*
6. *The degree to which psoriasis affected other (nonwork) regular activities (0–10).*

The recall period for the questions 2 to 6 is seven days. Four main outcomes can be generated from the WPAI and expressed in percentages by multiplying the following scores by 100:

1) Absenteeism: percent work time missed due to psoriasis = Q2/(Q2 + Q4) for those who were currently employed.

2) Presenteeism: percent impairment while working due to psoriasis = Q5/10 for those who were currently employed and actually worked in the past seven days.

3) Absenteeism plus presenteeism: percent overall work impairment due to psoriasis Q2/(Q2 + Q4) + ((1 - Q2/(Q2 + Q4)) × (Q5/10)) for those who were currently employed.

4) Activity impairment: percent activity impairment due to psoriasis Q6/10 for all respondents. For those who missed work and did not actually work in the past seven days, the percent overall work impairment due to psoriasis will be equal to the percent work time missed due to psoriasis.

For a sample of the English version of the WPAI:PSO please refer to Section 15.1.3 (Appendices).

- **Patient Satisfaction with the Overall Control of Psoriasis achieved with the Current Systemic Treatment**

  Patient's satisfaction with overall control of psoriasis achieved with his/her current treatment will be assessed using a simple, single-item 7-point Likert-type scale ranging from completely dissatisfied to completely satisfied (completely dissatisfied, mostly dissatisfied, somewhat dissatisfied, either satisfied or dissatisfied, somewhat satisfied, mostly satisfied, completely satisfied).

9.6.3 Administration of PROs

For the purposes of the current study, the validated local language versions of DLQI, EQ-5D-5L, WPAI:PSO, as well as the 7-point Likert-type scale for the assessment of the satisfaction with treatment will be administered to the patients via a paper-and-pencil self-administered format. The scores/answers will be subsequently transcribed into the eCRF (in the corresponding screens/fields) directly by the participating investigators.

The questionnaires shall be provided to the patients before completing any other procedures or clinical exam at the study visit and prior to being informed about the state of their disease and any changes in the current treatment. This ensures that the interaction between the

respondent and other health care professionals does not influence the patient's responses. The patient will be provided with instructions and a quiet and comfortable place to complete the questionnaires. The respondent should be alone when completing these PROs. Spouses or other accompanying individuals should wait in a separate area during the PROs administration. This minimizes any influence on the respondent's answer and ensures the PROs responses reflect the patient's perspective, and not someone else's.

When the respondent has completed the questionnaires, the study physician shall review them to ensure all questions have been answered. If there are any missing questions, he/she shall point them out to the respondent so they may be completed. However, respondents may omit any question they do not feel comfortable answering.

In order to protect subject confidentiality the name of the patient will not be mentioned on the questionnaires.

9.7 Study Size

Overall approximately 630 psoriatic patients are planned to be included in the study by approximately 50 sites in Bulgaria, Estonia, Hungary, Latvia, Lithuania, Romania and Russia.

This study's primary aim is purely descriptive in nature and is not planned to reject or affirm any formal statistical hypothesis. The sample size calculation has been based on the study's primary endpoint, which is the determination of the absolute PASI score as assessed by the participating physicians at the study visit.

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. In view of the cross-sectional and retrospective study design and the fact that the study's primary outcome measure strictly involves the physician-assessed disease severity through the estimation of PASI score at the single study

visit and that this information is expected to be collected for all enrolled eligible patients, a non-evaluable/drop-out rate has not been accounted for.

9.8 Data Management

The study data collection will be carried out through eCRFs which will be provided by AbbVie via a WBDC system, and through paper-and-pencil self-administered PROs.

Each center will document patient data in the eCRF. The investigator or delegated staff must complete the eCRF. Neither AbbVie nor any agents acting on behalf of AbbVie may complete the eCRF.

Diagnostic measures and observations routinely performed in patients included in this study will be entered by the researcher or staff under his/her supervision into the eCRF provided by AbbVie, according to the protocol. Only data specified in the protocol will be submitted to AbbVie.

The designated Clinical Research Organization (CRO) that will undertake the design, web hosting and help-desk support of the eCRF will follow its own internal Standard Operating Procedures (SOPs) that have been reviewed and approved by AbbVie, and will adhere to all applicable data protection regulations and requirements with regard to electronic records and database validation. The patients will be identified by patient identification number, site number, and study identification number.

Data (including those recorded in the paper PROs) will be entered in the eCRFs by the study personnel at the study site, according to the Investigator Instructions Manual, and they will be automatically saved to a central database with changes being tracked to provide an audit trail. When data have been entered, reviewed and edited, the Investigator shall sign the e-CRF electronically as per the agreed project process and data will be locked to prevent further editing after the completion of the proper data cleaning session by the delegated data management team.

Query management will be performed through built-in query management functionality that will be incorporated into the WBDC system.

Prior to the onset of data management activities, a detailed data management plan (DMP) and a data validation plan (DVP) will be issued describing the procedure to be followed for processing all collected study data in order to ensure they are valid, complete and accurate for statistical analysis.

In addition, aiming at ensuring the expected quality of data, a thorough data cleaning session will be applied. When all data have been properly validated and the quality control procedure has been completed, a declaration of database lock will take place so that it can be confirmed that all important actions have been properly performed.

Furthermore, prior to database lock and prior to the initiation of any statistical analysis activities a comprehensive statistical analysis plan (SAP) will be drafted. The SAP will also include information regarding the statistical software(s) to be used for the analysis of the study data and any data imputation methods that may be applied.

For the purposes of statistical analysis and reporting, recorded terms of medical history and comorbidities will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology (the last updated version available at the onset of medical coding) in preferred term (PT) and system organ class (SOC). The recorded psoriasis-related and other concomitant medications (if needed) will be coded with the use of the Anatomical Therapeutic Chemical (ATC) Drug Classification dictionary of the WHO Collaborating Centre (WHOCC) for Drug Statistics Methodology.

9.9 Data Analysis

Statistical analyses will mainly be of descriptive nature and exploratory statistical tests will be only used in the context of examining the correlation between disease severity and HRQoL at enrollment, the potential association of patient, treatment and disease characteristics with the primary outcome measure, as well as the influence of confounding factors on the potential identified associations.

Statistical analysis and generation of tables and patient data listings will be performed using SAS® statistical analysis software (the most updated version at the time of analysis onset). Figures will be created by validated graph programs, such as SAS® and/or Microsoft Excel. Categorical variables will be presented in frequency tables, while summary statistics [number of patients with available observations (n_{pt}), number of missing data (n_{miss}) mean, standard deviation (SD), median, 25th and 75th percentiles, minimum (min) and maximum (max)] will be used for continuous variables.

In the context of the primary endpoint analysis, summary statistics of the absolute PASI score will be estimated and presented along with the 95% CI for the mean in the overall study population.

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; in the context of these analysis, only variables with a missing data rate not exceeding 10% will be included in the models. Model selection in multivariable analysis will be described in detail in the SAP.

Within the context of further investigating the association of factors of interest with the primary outcome variable, adjustment for potential confounders may be performed. The unadjusted (crude) and adjusted estimates along with the 95% CI will be assessed and presented. More details will be provided in the SAP.

All statistical analyses will be performed in the set of all eligible patients with available data. In addition, 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.

Subpopulations by current systemic treatment option may be formed:

i) according to whether or not the current systemic therapy includes a biologic agent either as monotherapy or combined with other non-biologic agent *(i.e., therapy containing biologic agent versus therapy not containing biologic agent);*
ii) *by type [i.e. monotherapy, or combination therapy of the following therapy types: conventional systemic agents, biologics (e.g., TNF inhibitors, IL-12/23 inhibitors, IL-17 inhibitors), oral small-molecules. e.g. inhibitor of PDE4]*.

The subpopulations by systemic treatment option will be formed with the aim to create medically sound subgroups with a sufficient number of patients that will allow for meaningful interpretation and will be based on the observed frequencies of systemic therapies at a drug class level actually received by the patients enrolled in the study.

Patients erroneously enrolled in the study (i.e., not fulfilling the eligibility criteria) will be excluded from all analyses of this study and any deviations from the protocol will be reported in detail in the clinical study report (CSR).

No imputation will be applied with the exception of partial dates. Details will be provided in the SAP.

All exploratory statistical tests will be two-sided and will be performed at a 0.05 significance level. Adjustments for multiplicity do not fall within the scope of this analysis; control of type I error is not required. In addition, it is noted that due to the short duration of the study no interim analysis is planned to be conducted.

9.10 Quality Control

Oversight of the study is the responsibility of AbbVie.

Proper quality control mechanisms and processes will be implemented in order to ensure data quality and integrity throughout the conduct of the study. All these procedures will be detailed in the study specific DMP, DVP and SAP.

The query management process for the eCRF-collected data will be handled on a real-time-basis through built-in edit and logic checks (validation rules) in the eCRF application. For PRO-collected data no queries will be issued. After all data have been properly validated, the quality control procedure has been completed and database lock has been declared, the extracted file will be transferred to AbbVie. Statistical analysis performance and CSR development will be performed by a designated CRO.

Statistical programming performed to generate the results as well as all-related documents and forms will be archived electronically.

9.11 Limitations of the Research Methods

The main foreseen limitations for this study are attributed to its cross-sectional and retrospective design, and mainly involve systematic errors that may compromise its internal validity and primarily include inherent patient selection (sampling), confounding and information (misclassification) bias.

In order to mitigate confounding due to the potential of patient selection bias, 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 pre-specified study recruitment period. In addition, physicians will be requested to provide documentation of the screening process results for both consented and non-consented patients. In regards to the eligible patients who decline to participate in the study, date seen, age range, gender, and reason(s) for not participating will also be collected.

Moreover, physicians may be inclined to include only their “best” patients in the cohort or to act favorably towards including patients treated with an AbbVie product in the study. The risk of such bias will be minimized by offering comprehensive training to the physicians on the goal and aims of the study with clear instructions and guidance on the methodological requirements regarding patient sampling. This risk is also reduced by utilization of consecutive sampling, as stated above. Moreover, a ‘patient identification and

enrollment log' will be used to record all potentially eligible patients, i.e., patients who meet study selection criteria regardless of whether or not they agree to participate in the study.

The possible influence of confounding factors on the association of the protocol-defined factors with the study primary outcome (i.e., absolute PASI at enrollment) will be accounted for in the statistical analyses by the use of robust multivariable analyses.

With regard to patient information/recall bias that may be introduced by the collection of data pertaining to PROs, this will be mitigated through the use of widely used PROs that employ a relatively short-term (i.e., one week for the DLQI and the WPAI:PSO) or no recall period (for the EQ-5D-5L). In addition, the self-administered PROs including the Likert-type scale for the assessment of patient satisfaction with current treatment shall be completed by the patients themselves before the performance of any study-specific procedure(s) or clinical assessment(s) and prior to being informed about the state of their disease and any changes in the current treatment (where applicable), in order to avoid introducing any response bias.

Missing data impact the precision of the estimates and can bias the descriptions if not missing completely at random. The risk of missing data is accounted for by the use of an eCRF. Furthermore, regarding the general linear models, only variables with a missing data rate not exceeding 10% will be included in the multivariable models, in order to control for such bias in the derived estimations.

Internal validity of the outcomes will further be safeguarded to the extent feasible with the implementation of appropriate source data verification and quality assurance measures, as described in the relevant Section 9.10.

With regard to the external validity, generalizability of the study outcomes will be empowered by enrolling patients from geographically diverse locations throughout Central and Eastern European countries with a non-limiting set of clinical characteristics accounting for variations in medical practice paradigms. Generalizability of the findings will also be assessed by the 'patient identification and enrollment log'.

9.12 Other Aspects

9.12.1 Ethical Conduct of the Study

The guidelines for GPP in non-interventional studies of the International Society for Pharmacoepidemiology [67] will be respected, as well as the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [68] where applicable, the European General Data Protection Regulation and any applicable local laws and regulations. This study does not fall within the scope of Good Clinical Practice (GCP) standards. Any CA and IRB/IEC notification or approval will be obtained prior to the initiation of trial as necessary per local regulations.

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9.12.2 Source Documents and Records Storage and Retention

The Investigator should ensure that only appropriately qualified persons are delegated with duties associated with this study.

During the study and after termination of the study -including study's early termination- the Investigator must maintain copies of all documents and records relating to the conduct of the study.

This documentation includes, but is not limited to, protocols, eCRF archivals, patient source data, IRB approval letters, ICFs, Investigator's curricula vitae.

Source documents are original documents, data, and records from which the patient's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, paper PRO questionnaires, microfiches and radiographs, and physician's notes. All information entered in the eCRF must be traceable to these source documents in the patient's file except for the data for which the eCRF will serve as the source document and are described in Section 9.6. The Investigator must also keep the original informed consent form signed by the patient. The Investigator

must provide AbbVie (or designee) access to all relevant source documents to confirm their consistency with the eCRF entries. No information in source documents about the identity of the patients will be disclosed.

Patient files and other source documents must be kept for the maximum period of time permitted by the hospital/clinic, or as specified below. The study monitor must be consulted if the Investigator wishes to assign the files to someone else, remove them to another location, or if he/she is unable to retain them for the specified period.

The Investigator must retain study records for the amount of time specified by applicable laws and regulations. At a minimum, study records must be retained for the amount of time specified by the standing legislation, i.e., study records must be retained for at least 5 years after study completion. These documents may be retained for a longer period if required by AbbVie and this period and method of retention will be agreed to separately between the study site and the study Investigator. The Investigator should consult with the study monitor prior to discarding study's and/or patient's files.

9.12.3 Training of Study Site Personnel

The Principal Investigator will ensure that appropriate training relevant to the study is provided to all of the staff involved, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will also maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.12.4 Patient's Identification Code

For the identification of the patients during the conduct of the study and following its completion, the participating physician is responsible for maintaining a file with Patient Identification Codes for patients of his/her site (the patient identification and enrollment log). The file will be reviewed by AbbVie for completeness. The patient identification and

enrollment log will be treated as confidential and will be filed by the participating physician in the study file. To ensure patient confidentiality, no copy will be made.

All reports and communications relating to the study will identify participating patients by an anonymized 7-digit patient identification number that will be compiled by 2-letter country code, the 3-digit investigator site number and a 2-digit sequential number indicative of the series of patient inclusion in the specific study site.

9.12.5 Patient's Confidentiality

By signing this protocol, the Investigator agrees to treat all patient data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

The confidentiality of patient data will be maintained at all times and no documents containing the patient's name or other identifying information will be collected by AbbVie. It may be necessary for the AbbVie's representatives, the IRBs and regulatory authority representatives to have direct access to the patient's medical records. If study documents need to be photocopied during the process of verifying eCRF data, the patient will be identified by a unique code only; full names/initials and other identifying information will be masked.

By signing this protocol, the Investigator also affirms to AbbVie that information provided to the Investigator by AbbVie will be maintained in confidence and will be divulged only as necessary to the IRBs and institution employees directly involved in the study. IRB members and employees also understand the confidentiality requirements for any information divulged to them. The data generated by this study will be considered confidential by the Investigator, except to the extent that it is included in a publication as agreed in the publication policy of this protocol.

By signing the ICF, the patient accepts being informed of the following:

- The kind of personal information (data) that will be collected from participants in this study
- The persons that have access to the study information
- The persons that may use or disclose that information
- The rights of the participant pertaining to the potential revoke of his/her authorization for use of their personal data.

The collection and processing of personal data from patients enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. These data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration will be put in place.

9.12.6 Monitoring

AbbVie or designee will perform on-site monitoring visits, if needed, as frequently as necessary for this type of clinical research and according to local regulations.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. The monitor will contact the participating physician on a regular basis during the study to provide feedback on the study conduct.

9.12.7 Audits and Inspections

AbbVie may perform audit(s) of the study files at the study sites in order to ensure compliance with the study requirements, the GPP guidelines and the standing regulatory requirements.

In addition, the competent authorities may also inspect the sites at any time during the conduct or following the completion of the study. In case of an audit or inspection, the Investigator (and the institution) shall agree to permit the auditor(s) and inspector(s) to have direct access to all relevant documents and to provide adequate time, both he/she and his/her staff, for the discussion regarding any findings/major issues.

Patients shall be informed that properly authorized staff of AbbVie or the regulatory authority may inspect their medical files.

Patient data will remain confidential during the study and following its completion, and they will not be disclosed to any non-authorized third parties.

9.12.8 Study Completion/Termination

The study will be considered completed with the last visit within the study for the last patient participating in the study.

AbbVie reserves the right to close a participating site for data collection or to terminate the study at any time for any reason at the sole discretion of AbbVie.

The IRB of the participating sites will be notified about the end of the study or early termination of the study, unless otherwise mandated by the national regulations governing the conduct of such type of studies which may have been altered by the time of study completion.

10.0 Protection of Human Subjects

This study will be run in compliance with local laws and regulations. Notification/submission to the responsible Ethics Committee, Health Institutions and/or Competent Authorities will be performed as required by local laws and regulations (see Country Information page [Section 12.0]).

Written informed consent will be obtained prior to patient inclusion. In particular, prior to the conduct of any study-related activity, the Investigator must provide the patient with oral and written information about the study in a form that the patient can read and understand. The Investigator shall explain to the candidate participant patient the study purpose/objectives and the procedures to be followed during the conduct of this non-interventional study, as well as the potential risks and benefits and patient's rights and responsibilities due to his/her participation to the study. In addition, patients should be given the opportunity to ask questions and allowed time to consider the information provided. They must also be notified that they are free to discontinue from the study at any time. It is the Investigator's personal responsibility to obtain the written informed consent by the patient.

The ICF must be signed and dated by the patient. Following the obtainment of the written informed consent, the person who conducted the informed consent procedure shall sign and date the ICF. The patient must be provided with a copy of the signed ICF, while the original signed ICF must be filed by the Investigator.

11.0 Safety Reporting

Product-Related Events Including Adverse Reaction Reporting

This non-interventional study is not designed to identify or quantify a safety hazard relating to an AbbVie authorized product. For this reason safety data will not be collected.

If a patient reports a product-related event (e.g., suspected adverse reaction or product complaint) to his/her healthcare professional (HCP) during the data collection period or the healthcare professional identifies a product-related event, which is considered related to any AbbVie authorized product, the event should be reported to AbbVie. Any product-related events considered to be related to a non-AbbVie product should be reported in accordance with local laws and regulations to the relevant Regulatory Authority and/or drug marketing authorization holder.

The AbbVie contact details are specified in Country Information page (Section 12.0).

The retrospective portion of the study is based on secondary use of data previously collected from healthcare professionals for other purposes. Any suspected adverse reactions (adverse events considered to be likely related to an AbbVie product) identified during the course of the retrospective review of data should be reported to AbbVie clearly specifying the suspected adverse reaction was identified during retrospective review in an AbbVie non-interventional study. Any suspected adverse reactions considered to be related to a non-AbbVie product should be reported in accordance with local laws and regulations to the relevant Regulatory Authority and/or drug marketing authorization holder.

11.1 Patient Reported Outcomes and/or Quality of Life Questionnaires

PRO including QoL questionnaires data are not considered a potential source of adverse events for the purposes of this study. However, the HCP should review the PRO or questionnaire(s) data. If the HCP identifies a product-related event (such as a suspected adverse reaction), and if determined to be related to an AbbVie authorized product, the event shall be reported to AbbVie.

11.1.1 Adverse Reaction Definition

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an adverse event or not. Any worsening of a pre-existing condition or illness is considered an AE and should be reported as a new AE

11.1.2 Serious Adverse Event Definition

If an adverse event meets any of the following criteria, it is considered a serious adverse event (SAE):

Death of Patient	An event that results in the death of a patient.
Life-Threatening	An event that, in the opinion of the treating physician, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the patient's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.

Congenital Anomaly	An anomaly detected at or after birth or any anomaly that result in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

11.1.3 Serious and non-serious Adverse Event Reporting

- For **serious adverse events** from patients using an AbbVie product - notify AbbVie within 24 hours of the physician becoming aware of the event.
- For **nonserious adverse events** from patients using an AbbVie product – notify AbbVie within 15 calendar days of the physician becoming aware of the event, including "special situations."

11.1.4 Pregnancy Reporting

Pregnancy data is not being collected in the clinical database as part of this study.

If at any time you need to report a pregnancy occurrence in a patient or partner taking an AbbVie product, the physician can notify AbbVie using the contact details in Section 12 within 24 hours of the physician becoming aware of the pregnancy.

Pregnancy is not considered an adverse event. The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, is considered a serious adverse event and must be reported to AbbVie using the details in Section 12 within 24 hours of the site becoming aware of the event and to the relevant Regulatory Authority, as required by local laws and regulations.

The AbbVie contact details are specified in Country Information page (Section 12.0).

11.2 Product Complaint

11.2.1 Definition

A Product Complaint is any Complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be reported.

11.2.2 Complaint Reporting

Product Complaints concerning an AbbVie authorized product and/or device must be reported to AbbVie within 24 hours of the site's knowledge of the event using the AbbVie contact details specified in Country Information page (Section 12.0). All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. All complaints will be monitored on an ongoing basis.

Product complaints involving a non-AbbVie product and/or device should be reported to the identified contact or manufacturer, as necessary per local regulations.

Product Complaints may require return of the product with the alleged complaint condition (syringe, pen, etc.) as per standard process. In instances where a return is requested, every effort should be made by the physician to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

12.0 Country Information Page

AbbVie

The **CRYSTAL** Study – 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.

Sponsor:
Name Medical Director:
Address:
Address:
Country:
Phone:
Fax:

Safety/Pregnancy Reporting to:

E-mail:
Phone: Fax: :

Complaints Reporting to:

E-mail: Phone: Fax:

Shipment address for questionnaires:

Name:
Address:
Country:
Phone:
Fax:

Requirements for Non-Interventional Studies per Local Laws and Regulations:

Competent Authority approval ☐

Competent Authority notification ☐

Competent Authority involvement not required ☐

Ethics Committee approval ☐

Ethics Committee notification ☐

Ethics Committee involvement not required ☐

Written Patient Informed Consent required: ☐ No* ☐ Yes

*Written Patient Authorization to Disclose Data still required.

Regulatory requirements, other (if applicable):

Name of Affiliate Medical Director, Affiliate Medical Director

Signature Date

13.0 Plans for Disseminating and Communicating Study Results

At the end of the study, a report or publication will be written by AbbVie. This report/publication will contain a description of the objectives of the study, the methodology and its results and conclusions. The completed eCRFs, questionnaires and the final study output are the confidential property of AbbVie and may not be released to unauthorized people in any form (publications or presentations) without the express written approval from AbbVie.

The publication strategy and the authors' list will be agreed between the Medical Department of AbbVie and the participating Investigators. Publications will comply with the International Committee of Medical Journal Editors (ICMJE) guidelines, and the publication procedure of any relevant to the present study data will be determined based on the Uniform Requirements for Manuscripts Submitted to Biomedical Journals of the ICMJE.

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15.0 Appendices

15.1 Patient-Reported Outcomes

15.1.1 Dermatology Life Quality Index (DLQI) (Sample of English Version)

DERMATOLOGY LIFE QUALITY INDEX

☐ **DLQI**

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	 Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒

Please check you have answered EVERY question. Thank you.

15.1.2 EQ-5D-5L (Sample of English Version [UK])

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about	☐
I have slight problems in walking about	☐
I have moderate problems in walking about	☐
I have severe problems in walking about	☐
I am unable to walk about	☐

SELF-CARE

I have no problems washing or dressing myself	☐
I have slight problems washing or dressing myself	☐
I have moderate problems washing or dressing myself	☐
I have severe problems washing or dressing myself	☐
I am unable to wash or dress myself	☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities	☐
I have slight problems doing my usual activities	☐
I have moderate problems doing my usual activities	☐
I have severe problems doing my usual activities	☐
I am unable to do my usual activities	☐

PAIN / DISCOMFORT

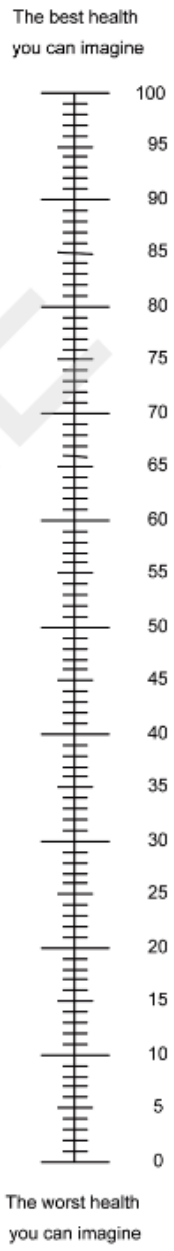
I have no pain or discomfort	☐
I have slight pain or discomfort	☐
I have moderate pain or discomfort	☐
I have severe pain or discomfort	☐
I have extreme pain or discomfort	☐

ANXIETY / DEPRESSION

I am not anxious or depressed	☐
I am slightly anxious or depressed	☐
I am moderately anxious or depressed	☐
I am severely anxious or depressed	☐
I am extremely anxious or depressed	☐

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



15.1.3 Work Productivity and Activity Impairment Questionnaire:Psoriasis V2.0 (WPAI:PSO) (Sample of English Version [UK])

The following questions ask about the effect of your psoriasis on your ability to work and perform normal daily activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____NO _____YES
   If NO, tick "NO" and skip to question 6.

The next questions refer to the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your psoriasis? *Include hours you missed on sick days, times you went in late, left early, etc., because of your psoriasis. Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as annual leave, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6)*

English-UK - WPAI:PSO V2.0 – 25/JUL/2011

5. During the past seven days, how much did your psoriasis affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If psoriasis affected your work only a little, choose a low number. Choose a high number if psoriasis affected your work a great deal.

Consider only how much psoriasis affected productivity while you were working.

Psoriasis had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Psoriasis completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your psoriasis affect your ability to perform your normal daily activities, other than work at a job?

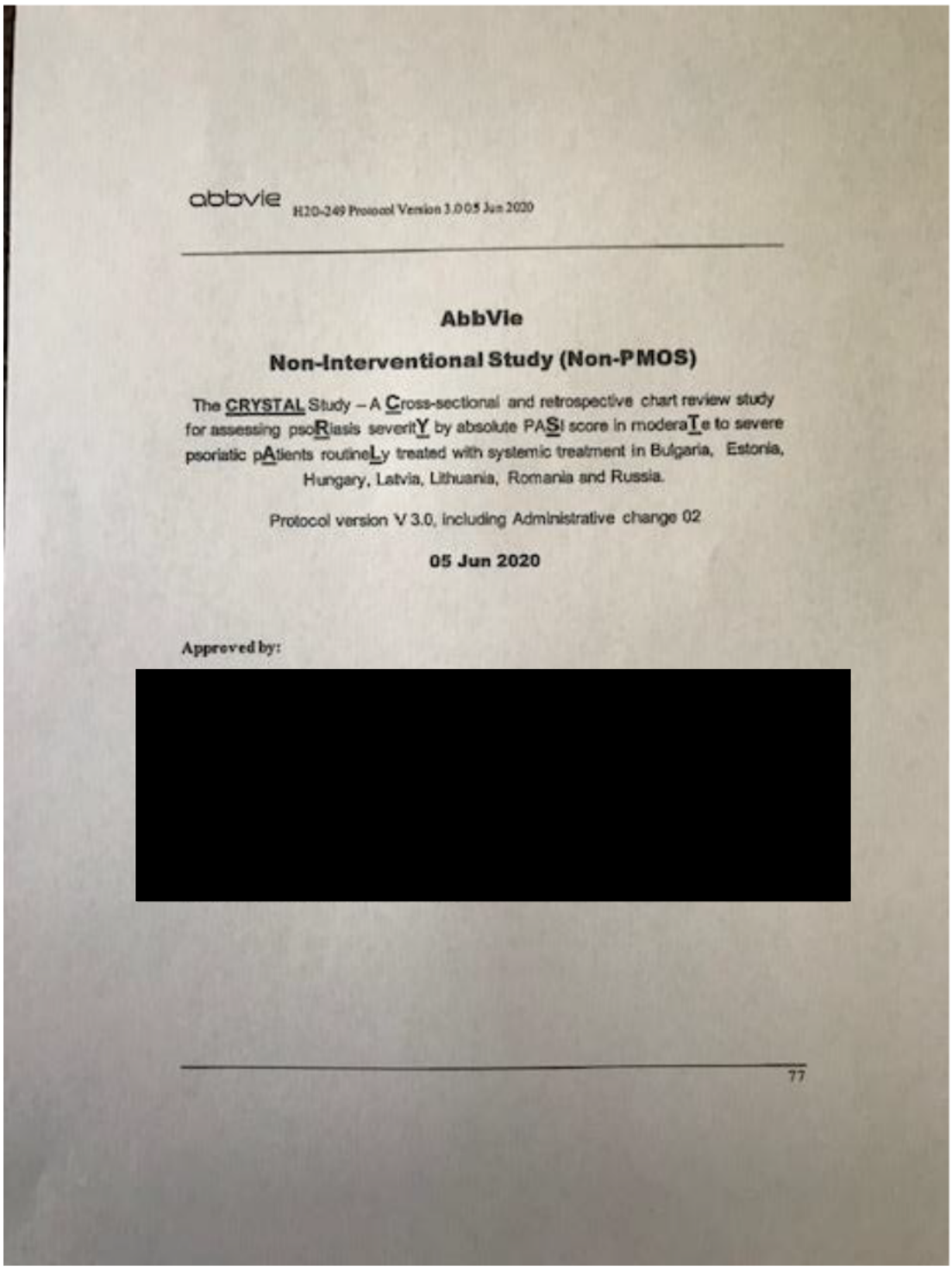
By normal activities, we mean the usual activities you perform, such as working around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could perform and times you accomplished less than you would like. If psoriasis affected your activities only a little, choose a low number. Choose a high number if psoriasis affected your activities a great deal.

Consider only how much psoriasis affected your ability to do your normal daily activities, other than work at a job.

Psoriasis had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Psoriasis completely prevented me from doing my daily activities

CIRCLE A NUMBER

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993 Nov;4(5):353-65.



abbvie H20-249 Protocol Version 3.0 05 Jun 2020

AbbVie

Non-Interventional Study (Non-PMOS)

The CRYSTAL Study – A Cross-sectional and retrospective chart review study for assessing psoRiasis severitY by absolute PASI score in moderaTe to severe psoriatic pAtients routineLy treated with systemic treatment in Bulgaria, Estonia, Hungary, Latvia, Lithuania, Romania and Russia.

Protocol version V 3.0, including Administrative change 02

05 Jun 2020

Approved by:

[redacted]

77