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PATIENT-REPORTED WELL-BEING IN VALUE-BASED CARE USING TILDRAKIZUMAB IN A REAL WORLD SETTING: PROTOCOL OF A MULTI-NATIONAL, PHASE IV, 1 COHORT PROSPECTIVE OBSERVATIONAL STUDY (THE POSITIVE STUDY)

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Manuscripts

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3 **PATIENT-REPORTED WELL-BEING IN VALUE-BASED CARE USING**
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5 **TILDRAKIZUMAB IN A REAL-WORLD SETTING: PROTOCOL OF A MULTI-**
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7 **NATIONAL, PHASE IV, 1-COHORT PROSPECTIVE OBSERVATIONAL STUDY**
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9 **(THE POSITIVE STUDY)**
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ABSTRACT

Introduction: Psoriasis is a chronic inflammatory skin disease that negatively impacts the quality of life of patients and their families. However, the most commonly used decision-making tools in psoriasis, Psoriasis Area and Severity Index (PASI), Physician Global Assessment (PGA) and Dermatology Life Quality Index (DLQI), do not fully capture the impact of psoriasis on patients' lives. In contrast, the well-established 5-item World Health Organization Well-being Index (WHO-5) assesses the subjective psychological well-being of patients. Moreover, while drug innovations became available for psoriasis, data on the impact of these therapies on patients' lives and their closest environment (family, physicians) is limited. This study will assess the effect of tildrakizumab, an interleukin-23p19 inhibitor, on the overall well-being of patients with moderate-to-severe psoriasis. Moreover, the long-term benefit of tildrakizumab on physicians' satisfaction and psoriasis patients' partners' lives will be evaluated.

Methods and analysis: This non-interventional, prospective, observational, real-world evidence study will involve multiple sites in Europe and approximately 500 adults with moderate-to-severe psoriasis treated with tildrakizumab. Each patient will be followed for 24 months. The primary endpoint is well-being measured by the WHO-5 questionnaire. Key secondary endpoints include Physician's Satisfaction and partner's quality of life (FamilyPso). Other endpoints will evaluate skin-generic quality of life (DLQI-R), Treatment Satisfaction Questionnaire for Medication (TSQM-9), Treatment-related Patient Benefit Index "Standard", 10 items (PBI-S-10), and work productivity and activity impairment (WPAI). Statistical analyses will be based on observed cases. Multiple imputation will be performed as a sensitivity analysis, and adverse events will be reported.

Ethics and dissemination: The study will be conducted according to the protocol, which received ethics committee approval and applicable regulatory requirements of each

1
2
3 participating country. The results will be disseminated through scientific publications and
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5 congress presentations.
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10 **Registration details:** NCT04823247.
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STRENGTHS AND LIMITATIONS OF THIS STUDY

- First clinical study in dermatology using the patient-reported well-being as the primary endpoint in accordance with the holistic definition of health by the World Health Organization (WHO)
- Innovative secondary endpoints such as physician's well-being, patient-defined benefit assessment and the impact of psoriasis on the patients' partner following a people-centred approach claimed by the WHO.
- Relevant sample size from different European countries.
- Patient's bias on self-perception due to the inclusion in a clinical study.
- Potential drop-outs or losses to follow-up due to the long observational period.

INTRODUCTION

Psoriasis is an immune-mediated, chronic relapsing inflammatory condition characterised by abnormal differentiation and proliferation of the epidermis affecting skin, nails, and joints [1]. The severity of psoriasis is profound as it includes physical and psychological components [2]. Increasing evidence suggest that psoriasis considerably affects the overall well-being of patients and their families [3], as well as their personal, social, and occupational life [4], often resulting in psychological distress and depression [5–7]. A Europe-wide survey examining quality of life reported that almost 77% of patients believed psoriasis negatively affected normal daily activities and well-being [8]. Moreover, a more recent survey showed that psoriasis patients generally report poor quality of life and physicians are often also not satisfied with their patients' treatment [9]. These studies highlight the need for a well-being evaluation strategy besides the available psoriasis severity scoring assessments [10]. Patient-reported outcomes (PROs) are being used with increasing frequency in clinical trials and provide valuable information on how psoriasis affects physical, social, and psychological aspects of patients' lives. However, the most commonly used decision-making tools in psoriasis, the clinician-reported Psoriasis Area Severity Index (PASI), Physician Global Assessment (PGA) and the patient-reported Dermatology Life Quality Index (DLQI), do not take into account the entire patient disease perspective, leading to misaligned perception between physicians and patients [11]. While the PASI and PGA track changes in psoriasis severity from a clinician's perspective [12,13], the skin-generic DLQI has been used to evaluate psoriasis symptoms and their impact on quality of life [14]. However, the use of the DLQI has been associated with several measurement problems related to age, gender difference, inadequate power to differentiate patients with mild illness, and underestimating patient's emotional status [15,16]. Furthermore, being a sum score and permitting to rate "not relevant" in 8 out of 10 items, DLQI has been shown to provide marked bias and to underestimate the burden of very severely affected

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3 patients[16]. Moreover, a systematic review on skin conditions has highlighted the critical need
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5 for psychiatric assessments in addition to the DLQI score for a full assessment of patient
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patients[16]. Moreover, a systematic review on skin conditions has highlighted the critical need for psychiatric assessments in addition to the DLQI score for a full assessment of patient psychological well-being [17,18].

Unmet needs at the time of biologics

Studies have indicated that a patient-oriented evaluation is critical for overall symptom assessment as physicians' indicators alone cannot capture the disease burden of psoriasis [19–21]. The advent of biologics as monotherapy or in combination with other topical or systemic medications significantly changed the treatment approach for psoriasis representing an advancement over topical treatments or traditional immunosuppressive therapies [22–24]. Biologics target specific components of the immune system and have shown a high benefit-to-risk ratio, high efficacy and acceptable safety profiles [25]. Further, more advanced biologics have been shown to be more cost-effective than first-generation drugs [26,27]. Monoclonal antibodies, selective for the interleukin (IL)-23p19 subunit inhibition, represent a new standard of treatment currently available for the long-term management of psoriasis [28]. Among these, tildrakizumab has demonstrated long-term efficacy and safety in the pivotal phase 3 studies (reSURFACE 1 and 2) comparing tildrakizumab versus placebo or etanercept for moderate-to-severe psoriasis [29]. However, while biologics are becoming a more important treatment option for individuals with psoriasis, current therapy goals and PROs in dermatology do not fully capture the impact of this therapy on patients' and physicians' well-being [30,31]. Moreover, although several studies have shown that psoriasis significantly affects mental health [32,33], standard severity scores have been found to be very weakly associated with the overall well-being of these patients [34,35]. In practice, there is high need to translate patient burden to patients needs and then derive patient goals conjointly with the patient. Thus, understanding the needs and expectations of patients beyond measuring burden constitutes a fundamental part

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3 of treatment in psoriasis [36]. This is particularly important in sensitive conditions such as nail
4 and anogenital affections [37–39].
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8 **Well-being in psoriasis: clinical goals**

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10 Insights on the well-being of the patients are based on the patient's view of their condition, and
11 this concept is increasingly being embraced as a more comprehensive outcome in line with a
12 holistic view and people-centred perspective, but still undervalued in traditional PROs. Well-
13 being is a holistic multifaceted concept that in a study context describes “to what extent patients
14 will get their healthy lives back”, where mental, physical, and social functioning are
15 interdependent [40]. According to the World Health Organisation (WHO), the ultimate goal of
16 therapy in chronic diseases such as psoriasis is achieving well-being [41]. Nevertheless, well-
17 being has been rarely measured in dermatology so far. A recent study concluded that the DLQI
18 primarily measures physical impairment associated with negative emotions and, thus, provides
19 only a limited evaluation of well-being [42]. Thus, assessing well-being or specific dimensions
20 of well-being can contribute to a holistic evaluation of patients' health in accordance with the
21 WHO's holistic definition.
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39 **Innovative endpoints in this study**

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41 To assess patient well-being this study will apply the 5-item WHO Well-being Index (WHO-
42 5), a widely used questionnaire assessing psychological health-related well-being in a variety
43 of chronic diseases such as diabetes, cardiovascular disease, cancer, and depression [43]. For
44 the first time, WHO-5 will be used as a primary endpoint in patients with psoriasis to investigate
45 the improvements that tildrakizumab can achieve on patients' well-being in a real-world setting.
46 Moreover, building a positive cross-talk environment between healthcare professionals and
47 patients is critical. A meta-analysis study including 400 publications reported a higher quality
48 of life and overall improved treatment outcome when patients had higher trust in their physician
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3 [21], underlining how physician's well-being is essential as it can improve patients' satisfaction
4 and interpersonal aspects of care [22]. Patient's behaviour, in turn, can affect physicians' well-
5 being, including unrealistic expectations, aggression, or by developing family-like
6 relationships, resulting in emotional detachment and burnout [23]. As there is no complete
7 correlation between patient- and physician-reported outcome measures, both PROs and
8 physician-reported scores should be considered when assessing treatment outcomes [24]. In this
9 study, the 'Physician's satisfaction' score will be exploited as an innovative tool to investigate
10 the impact of the psoriasis treatment process on physicians' wellbeing. Furthermore,
11 information on the impact of psoriasis on patients' families, particularly partners, is also
12 lacking, even though the impact of skin disease on family members or partners of patients
13 should be measured while evaluating the burden of psoriasis [3]. Thus, this study will include
14 the questionnaire FamilyPso [44], enabling physicians to better understand the impact of
15 psoriasis as a lifelong chronic disease on partners. This study will provide novel insights into
16 the dimensions of patients' perspectives and their overall state of well-being using a holistic
17 patient-partner and physicians-centred approach. The current study is designed to investigate
18 patient-reported well-being using tildrakizumab in a real-world setting, as well as the impact
19 on their closing environment, including partners and physicians, to provide a more
20 comprehensive overview of people-centred healthcare and their overall state of well-being.
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METHODS AND ANALYSIS

The primary objective is to assess the effect of tildrakizumab on the overall well-being in patients with moderate-to-severe psoriasis using the WHO-5 questionnaire. Secondary objectives include: to evaluate the long-term benefit of tildrakizumab on physician's satisfaction (Physician's Satisfaction Questionnaire) and the impact of psoriasis on patients' partners (FamilyPso questionnaire); to assess the long-term benefit of tildrakizumab reported by patients in terms of skin-generic quality of life (DLQI-R), treatment satisfaction (TSQM-9) and treatment-related benefits (PBI-S-10), work impairment due to psoriasis (WPAI:PSO) and extent of the skin manifestations using the "Heat map" in a subgroup of patients; to correlate the change of WHO-5 with patients' health-related quality of life (HRQoL) and patients' treatment benefits; to assess the control of skin manifestations (absolute PASI) and its impact on patients, physician's satisfaction and on partners of patients; to describe the socio-demographic and clinical profile of the patients being treated with tildrakizumab, according to the routine clinical practice; and to assess the safety and tolerability of tildrakizumab in a real-world setting. Exploratory objectives are to assess the impact of tildrakizumab on PGA of the skin manifestations and to assess the concordance between patients and physician's satisfaction regarding response to the treatment with tildrakizumab.

Study design

This is an ethics-approved, multi-national, Phase IV, 1-cohort prospective observational study planned to be conducted in multiple sites in several countries (e.g., Austria, Belgium, France, Germany, Italy, Spain, Switzerland, The Netherlands, and United Kingdom [UK]) to assess patient-reported well-being using tildrakizumab in a live setting. The study design is summarised in **Figure 1**.

Study population

The study population will comprise a minimum of 338 patients with moderate-to-severe plaque psoriasis who need systemic biologic therapy and qualify for treatment with an IL-23p19 inhibitor in real-world clinical practice. Consecutive patients satisfying all the inclusion criteria and none of the exclusion criteria shown in **Table 1** to be eligible for participation will be offered participation. Recruitment will be competitive across all countries participating in the study (i.e., no fixed number of patients per country).

Table 1. Eligibility criteria

Inclusion criteria	
1	Patient with diagnosis of moderate-to-severe chronic plaque psoriasis documented in the medical chart.
2	Patient who needs systemic biologic therapy and qualifies for treatment with an IL-23p19 inhibitor. Tildrakizumab must be the anti-IL-23p19 selected therapy before including the patient in the study.
3	Patient aged 18 years or older at the time of patient recruitment.
4	Patient who has provided written informed consent (if required by country regulations).
Exclusion criteria	
1	Patients unable to comply with the requirements of the study or who, in the opinion of the study physician, should not participate in the study.
2	Patients included in a clinical trial.

IL, interleukin.

Endpoints

Study endpoints cover outcomes reported by patients, their partners, and physicians. The primary endpoint is to assess the overall health-related well-being (evaluated through WHO-5 questionnaire) in patients treated with tildrakizumab according to the marketing authorization and routine clinical practice at the long-term. The secondary endpoints are: physicians' satisfaction evaluation through a composite survey with 16 items (10 generic professional quality of life items and 6 items related to the biological treatment); partner well-being evaluation through the FamilyPso questionnaire; patient's perspective on tildrakizumab long-term benefit evaluation through the (i) skin-generic quality of life questionnaire (DLQI-R), (ii) Treatment Satisfaction Questionnaire for Medication (TSQM-9), (iii) Treatment-related Patient

Benefit Index “Standard”, 10 items (PBI-S-10), (iv) Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI:PSO), (v) skin manifestations distribution (patient’s grid) and (vi) the Numeric Rating Scale (NRS) for itch, pain, joint pain, and fatigue assessments; disease control evaluated through the absolute PASI; description of the sociodemographic (age, gender, educational and working status, etc.) and clinical (location of moderate-to-severe psoriasis, comorbid disease, laboratory tests, etc.) characteristics; adverse events (AE) reported during the use of tildrakizumab. The exploratory endpoints are: the control of the skin manifestation evaluation through the PGA; Patient’s and physician’s opinion about tildrakizumab treatment in relation to the therapeutic objectives’ evaluation through the Patient’s and physician’s questionnaire (**Table 2**).

Table 2. Endpoints of the study

	Patient reported outcomes	Partners reported outcomes	Physician reported outcomes	Patient and physician reported outcomes
Primary endpoint	- WHO-5			
Secondary endpoint	- DLQI-R - TSQM-9 - PBI-S-10 - WPAI: PSO - Patient grid - NRS (itch, pain, joint pain, fatigue assessments) - Sociodemographic and clinical characteristics - AEs during tildrakizumab use	- FamilyPso	- Physicians’ satisfaction - Absolute PASI	
Exploratory endpoints			- PGA	- Patient’s and physician’s questionnaire - Patient’s and physician’s satisfaction of

				being part of the study
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AE, adverse event; DLQI-R, Dermatology Life Quality Index-Revised; NRS, Numeric Rating Scale; PASI, Psoriasis Area Severity Index; PBI-S-10, Patient Benefit Index “Standard”, 10 items short form; PGA, Physician Global Assessment; TSQM-9, Treatment Satisfaction Questionnaire for Medication ;WHO-5, World Health Organization-Five Well-being Index; WPAI:PSO, Work Productivity and Activity Impairment Questionnaire: Psoriasis.

Data sources and collection

All data will be collected prospectively from the medical charts and entered directly into the electronic data capture system. The study will include both variables extracted from the medical chart and obtained directly from the patients. No visits or examinations, laboratory tests, or procedures are mandated or recommended as part of this study. The data collection schedule is shown in **Table 3**.

Table 3. Data collection schedule

	Baseline visit	Follow-up visit (at 16 and 28 weeks, 12 and 18 months after baseline visit)	Final visit (24 months from baseline)	Early termination visit
Patient characteristics and demographics (including date of ICF signature)	X		X ^a	X ^a
Disease characteristics (diagnosis date, type of psoriasis, severity of psoriasis)	X			
Laboratory test (if it is available)	X	X	X	X
Comorbidities	X	X	X	X
Concomitant medication	X	X	X	X
Drug therapy history	X			
Tildrakizumab drug therapy (dose)	X	X	X	X
PASI	X	X	X	X
Heat map/patient’s grid (subgroup of patients)	X	X	X	X
Adverse Event reporting	X	X	X	X

	Baseline visit	Follow-up visit (at 16 and 28 weeks, 12 and 18 months after baseline visit)	Final visit (24 months from baseline)	Early termination visit
Questionnaires				
WHO-5	X	X	X	X
DLQI-R	X	X	X	X
PBI-S-10	X	X	X	X
TSQM-9		X	X	X
WPAI:PSO	X	X	X	X
FamilyPso	X	X	X	X
NRS (itch, pain, joint pain, fatigue)	X	X	X	X
Patient's and Physician's satisfaction of being part in the study (open field question)	X		X	X
PGA	X	X	X	X
Physician's satisfaction	X	X	X	X
Patient's and physician's questionnaire		X	X	X

DLQI-R, Dermatology Life Quality Index-Revised; ICF, informed consent form; NRS, Numeric Rating Scale; PASI, Psoriasis Area Severity Index; PBI-S-10, Patient Benefit Index "Standard", 10 items short form; PGA, Physician Global Assessment; TSQM-9, Treatment Satisfaction Questionnaire for Medication ;WHO-5, World Health Organization-Five Well-being Index; WPAI:PSO, Work Productivity and Activity Impairment Questionnaire: Psoriasis; a, Undefined.

Questionnaires

All the questionnaires included in the study have validated translations according to international guidelines from the original language to the official languages in the participating countries.

Primary endpoint:

1. The 5-item World Health Organization Well-being Index (WHO-5): The WHO-5 is a generic global rating scale measuring subjective well-being containing positive statements. The respondent is asked to rate how well each of the 5 items applies to him or her when considering the last 14 days. Each of the 5 items is scored from 5 (all of the time) to 0 (none of the time). The raw score therefore theoretically ranges from 0

(absence of well-being) to 25 (maximal well-being). To standardize the score on a scale from 0 (absent) to 100 (maximal), it is recommended to multiply the raw score by 4 [43].

Secondary endpoints:

2. Dermatology Life Quality Index-Relevant (DLQI-R): The DLQI-R is a recently developed scoring that adjusts the total score of the questionnaire for the number of 'not relevant' responses indicated by a patient. It is a self-administrated questionnaire validated as a dermatology-specific quality of life instrument. It includes 10 items to assess patient's HRQoL during the previous week on a 4-point scale, indicating 'not at all', 'a little', 'a lot' and 'very much', respectively. For each patient, the DLQI-R score is estimated as a sum score of the original DLQI score replacing items rated "not relevant" by the mean of the other items [45].
3. Patient Benefit Index "Standard", 10-item short form (PBI-S-10: 10 items describing treatment goals of patients with skin diseases. Before treatment, these goals are rated on a 5-point Likert-scale (0="not at all", 4="very") according to their perceived relevance (PNQ). Alternatively, patients can state that a goal "does not apply" to them. In the course of treatment, patients are asked to express the achievement of these 10 treatment goals (treatment benefit) on the same 5-point Likert-scale (PBQ), again with the opportunity to state that the goal did not apply [46]. An overall index of patient benefits (PBI) is calculated by adding the single weighted benefits to a sum score reaching from 0=no patient benefit to 4=very strong patient benefit.
4. Treatment Satisfaction Questionnaire for Medication (TSQM-9): It is a self-administrated questionnaire that measures patients' drug therapy satisfaction considering the last two or three weeks or since the last time the patient took the medication. It consists of 9 statements distributed in 3 domains: efficacy (3 items),

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3 convenience (3 items) and global satisfaction (3 items). Responses are measured on a
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5 Likert scale of 5 or 7 points [47,48].
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8 5. Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI: PSO): It
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10 is a self-administrated questionnaire that measures the impact on the work productivity
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12 in patients with psoriasis considering the last seven days. The questionnaire contains 6
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14 items with dichotomous response options [49].
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17 6. Numeric Rating Scale (NRS) (itch, pain, joint pain, fatigue): It is a self-administrated
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19 questionnaire to assess patients' itch severity, pain, joint pain and fatigue. The
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21 questionnaire has a single-item that describes the worst level of itching, joint pain and
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23 fatigue, respectively, due to psoriasis in the past 24h [50].
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26 7. FamilyPso: It is a self-administrated questionnaire to assess the burden on partners of
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28 patients with psoriasis. The questionnaire has 15 items divided in 5 factors: 1) Perceived
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30 strain by social reactions to the partner's psoriasis; 2) Strain caused by cleaning; 3)
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32 Acute emotional strain attributed directly to the psoriasis; 4) Restrictions of social life;
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34 5) General emotional strain. The items are scaled in a 5-point Likert format: 0='not
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36 true', 1='somewhat true', 2='moderately true', 3='quite true', 4='very true', with the
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38 supplementary option 'does not apply to me' [44].
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42 8. Patient's and physician's questionnaire: Survey of 10 questions elaborated for this
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44 project with the objective to assess the opinion of physicians and patients about
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46 tildrakizumab treatment in relation to the therapeutic objectives. The physician will
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48 respond according to his/her assessment in relation to the response to tildrakizumab
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50 treatment of each patient. Each item is scaled in a 5-points Likert format: 'strongly
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52 agree', 'agree', 'uncertain', 'disagree' and 'strongly disagree'.
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56 9. PASI: measure of psoriasis severity average to quantify psoriasis grade [51], combining
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58 an assessment of each psoriasis lesion graded on a 0-4 scale (0=none and 4=maximum)
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3 based on three parameters of the lesions including, erythema (redness), induration
4 (thickness), desquamation (scaliness) and on a weighted evaluation of the affected area
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6 (from 0=affecting 0% to 6=affecting 100%), dividing the body into four sections: head
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8 (10% of person's skin), trunk (30%), upper extremities (20%) and lower extremities
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10 (40%). Each area is scored by itself.
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15 10. Physician Global Assessment (PGA): A 5-point ordinal scale used to assess the severity
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17 of disease over the body including global, scalp, palmoplantar and nails. The scale
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19 ranges from 0 to 4 for global, scalp and palmoplantar assessment [52]:
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22 0= clear: no signs of psoriasis

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24 1= almost clear: only minimal plaque elevation, scaling, and/or erythema

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26 2= mild: slight plaque elevation, scaling, and/or erythema

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28 3= moderate: moderate plaque elevation, scaling, and/or erythema

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30 4= severe: very marked plaque elevation, scaling, and/or erythema
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33 For nails assessment, the scale ranges from 0 to 4:

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35 0= none: normal nail appearance

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37 1= mild: pitting and/or oil drops; mild disfigurement

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39 2= moderate: prominent visible pitting and/or oil drops, distal onycholysis
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41 with/without hyperkeratosis; moderate disfigurement
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44 3= severe: pronounced nail changes including pitting, oil drops, distal
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46 onycholysis with/without hyperkeratosis, onychodystrophy; substantial
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48 disfigurement
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51 4= very severe: severe distal onycholysis with/without hyperkeratosis and/or
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53 severe onychodystrophy; prominent disfigurement
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56 11. Physician's satisfaction: A composite survey with 16 items, 10 of them are generic
57
58 items and correspond to the compassion subscale of the ProQoL questionnaire [53]; and
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3 6 items were specifically created for this study regarding biological treatment. There are
4
5 5-point scales that reflect how frequently the physician experienced this thing in the last
6
7 30 days.
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10 12. Patient's and physician's satisfaction of being part of the study: open question to assess
11
12 the satisfaction that the participation on a clinical study may provide to the patients and
13
14 physicians.
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17 **Sample size calculation**

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20 A total sample size of 338 patients with baseline WHO-5 score ≤ 50 will provide a 95% power
21
22 to detect a difference of 10 points [43] in the absolute change from baseline in the WHO-5 total
23
24 score at week 24, assuming 50.5 as the standard deviation of the difference. This sample size
25
26 of 338 patients produces a two-sided 95% confidence interval with a precision of ± 5.4 points.
27
28 A conservative estimation assumes that 75% of the psoriatic population may have a baseline
29
30 WHO-5 score ≤ 50 [54]. Therefore, around 450 patients will have to be included in the study to
31
32 ensure the 338 patients previously described. Also considering a 10% drop out rate, the final
33
34 number of patients to be included will be approximately 500.
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39 **Data analyses and reporting**

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41 All data analyses will be performed using SAS[®] version 9.2 or higher (SAS Institute, Cary, NC,
42
43 USA). Descriptive analyses will be performed. Statistical analyses will be based on observed
44
45 cases. Multiple imputation will be performed as a sensitivity analysis. All AE verbatim terms
46
47 will be recorded and coded using the Medical Dictionary for Regulatory Activities (MedDRA).
48
49 Medication will be coded using WHO Drug Dictionary. Final analyses will be performed once
50
51 the data from all patients have been collected in the database, cleaned, and database lock has
52
53 occurred. Analyses will be performed overall and per country.
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58 **Patient and public involvement statement**

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3 Patients or the public were not involved in the design of the study, and will not be involved in
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5 the conduct, reporting, or dissemination plans of this research.
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ETHICS AND DISSEMINATION

This non-interventional study will be conducted in compliance with the protocol, all applicable regulatory requirements of the countries where the study is being conducted and the ethical principles of the latest version of the Declaration of Helsinki that are consistent with Good Pharmacoepidemiology Practices (GPP). Data protection and privacy regulations will be strictly observed in capturing, forwarding, processing, and storing patient data according to the Directive 95/46/EC on the protection of individuals and in compliance with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). The results of the POSITIVE study will be disseminated through one or more scientific manuscripts and may also be presented at medical congresses.

DISCUSSION

The lack of patient-oriented outcome measures for assessing the overall well-being of patients with psoriasis is becoming a concern in dermatology clinical practice and research. Psoriasis heavily affects the physical, psychological and social well-being of patients and that of their family members and partners, thus, beside clinical assessments, the full impact of psoriasis treatment on the patient and people around should be recognised. To our knowledge, the POSITIVE study is the first study to apply the WHO-5 as a primary endpoint to estimate the improvements on patients' well-being treated with tildrakizumab in a real-world setting. This study will measure the well-being of patients, their partners and of physicians, for a better understanding of the impact of psoriasis as a chronic disease on patients' and their close environment. The results of this study could potentially be added to the available psoriasis evaluation methods, and provide dermatologists with new tools to improve their own and patient's well-being enhancing patient-clinician relationships. The need to provide results from the POSITIVE study becomes essential given the WHO claim for people-centred healthcare and patient commitment. The POSITIVE study will significantly promote patients' involvement and awareness as recommended by the WHO global report on psoriasis [5], as the most common root for patient dissatisfaction is being poorly engaged in the treatment decision-making process. Limitations of the study will include potential bias and missing information or possible drop-outs or lost to follow-up in the last follow-up visits of the study because of the long observational period. Moreover, patients included in this study will have to be preselected to initiate tildrakizumab therapy before patient inclusion in the study. Finally, a limitation could be represented by patient-related bias on self-perception due to the inclusion in a clinical study.

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3 In summary, this prospective observation study constitutes an innovative people-centric
4 approach to investigate how intervention with tildrakizumab may improve the wellbeing of
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6 patients, their families, and healthcare professionals.
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CONTRIBUTORSHIP STATEMENT

All authors were involved in conception and study design. All authors provided edits, critiqued the manuscript for intellectual content, and approved the final manuscript.

COMPETING INTERESTS

MA has served as consultant for, or has been a paid speaker for clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including Abbvie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Eli-Lilly, GSK, Janssen-Cilag, Leo Pharma, Medac, Merck, MSD, Novartis, Pfizer, UCB, and Xenoport; **RS** has been an advisor and/or received speaker honoraria and/or received grants from AbbVie, Almirall, Beiersdorf, Janssen, LEO Pharma and Novartis; **ED** has the following conflict of interests: Advisory Board member, consultant, grants, research support, participation in clinical trials, honorarium for speaking, research support, with the following pharmaceutical companies: Abbvie/Abbott, Almirall, Amgen, Janssen-Cilag, Leo Pharma, Novartis, Pfizer, MSD-Schering-Plough, Celgene, Lilly, and UCB; **PL** received honoraria and/or grants as an investigator, speaker, and/or advisory board member for AbbVie, Almirall, Actelion, Celgene, Janssen, Lilly, Sanofi, Leo, UCB, and Novartis; **EdJ** has received research grants for the independent research fund of the department of dermatology of the Radboud University Medical Center Nijmegen, The Netherlands from AbbVie, Leo Pharma, Janssen Pharmaceuticals, Novartis, Pfizer, and UCB and has acted as consultant and/or paid speaker for and/or participated in research sponsored by companies that manufacture drugs used for the treatment of psoriasis including AbbVie, Almirall, Celgene, Galapagos, Janssen Pharmaceutica, Leo Pharma, Lilly, Novartis, Sanofi, and UCB. All funding is not personal but goes to the independent research fund of the department of dermatology of Radboud University Medical Center Nijmegen (Radboudumc), The Netherlands; **GF** has acted as speaker and consultant for AbbVie, Almirall, Eli Lilly, Leo Pharma, Janssen, Novartis, and UCB; **LN**

1
2
3 received consultation fees from Abbvie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly,
4
5 IBSA, Menarini, Janssen, Novartis, and Sanofi; **AN** declares being a consultant and advisor
6
7 and/or receiving speaking fees and/or grants and/or served as an investigator in clinical trials
8
9 for AbbVie, Almirall, Amgen, BMS, Boehringer Ingelheim, Celgene, Eli Lilly, Galderma,
10
11 GSK, LEO Pharma, Janssen-Cilag, MSD, Novartis, Pfizer, Sandoz, Sanofi, Serono and UCB;
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13 **JL** has been a speaker/advisor for and her institution received grants from AbbVie, Almirall,
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17 been an advisor, investigator, and/or speaker for Novartis, Janssen-Cilag, Lilly, eo-Pharma,
18
19 Celgene, Pfizer, UCB, Amgen, Almirall, MSD, and MEDAC; **SG** has been an advisor and/or
20
21 received speakers' honoraria and/or received grants and/or participated in clinical trials of the
22
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25 Amgen, Anaptys Bio, Argenx BV, AstraZeneca AB, Biogen Idec, Bioskin, Boehringer-
26
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28
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32
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34
35 employees of Almirall; **TO** has served as medical advisor for Almirall; **UM** has been an advisor
36
37 and/or received speakers' honoraria and/or received grants and/or participated in clinical trials
38
39 of the following companies: AbbVie, Aditxt, Almirall, Amgen, Aristeia, Boehringer-Ingelheim,
40
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58 **DATA SHARING STATEMENT**

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Not applicable.

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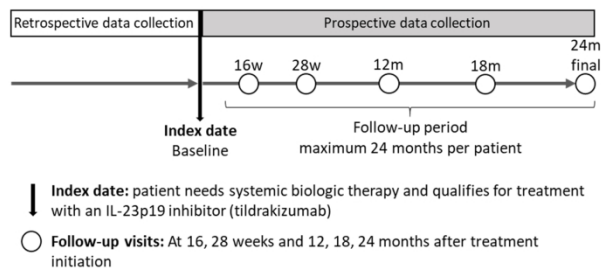
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FIGURES

Figure 1. Study design of the POSITIVE study

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BMJ Open

PATIENT-REPORTED WELL-BEING IN VALUE-BASED CARE USING TILDRAKIZUMAB IN A REAL WORLD SETTING: PROTOCOL OF A MULTI-NATIONAL, PHASE IV, 1 COHORT PROSPECTIVE OBSERVATIONAL STUDY (THE POSITIVE STUDY)

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Primary Subject Heading:	Patient-centred medicine
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5 **TILDRAKIZUMAB IN A REAL-WORLD SETTING: PROTOCOL OF A MULTI-**
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7 **NATIONAL, PHASE IV, 1-COHORT PROSPECTIVE OBSERVATIONAL STUDY**
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9 **(THE POSITIVE STUDY)**
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ABSTRACT

Introduction: Psoriasis is a chronic inflammatory skin disease that negatively impacts the quality of life of patients and their families. However, the most commonly used decision-making tools in psoriasis, Psoriasis Area and Severity Index (PASI), Physician Global Assessment (PGA) and Dermatology Life Quality Index (DLQI), do not fully capture the impact of psoriasis on patients' lives. In contrast, the well-established 5-item World Health Organization Well-being Index (WHO-5) assesses the subjective psychological well-being of patients. Moreover, while drug innovations became available for psoriasis, data on the impact of these therapies on patients' lives and their closest environment (family, physicians) is limited. This study will assess the effect of tildrakizumab, an interleukin-23p19 inhibitor, on the overall well-being of patients with moderate-to-severe psoriasis. Moreover, the long-term benefit of tildrakizumab on physicians' satisfaction and psoriasis patients' partners' lives will be evaluated.

Methods and analysis: This non-interventional, prospective, observational, real-world evidence study will involve multiple sites in Europe and approximately 500 adults with moderate-to-severe psoriasis treated with tildrakizumab. Each patient will be followed for 24 months. The primary endpoint is well-being measured by the WHO-5 questionnaire. Key secondary endpoints include Physician's Satisfaction and partner's quality of life (FamilyPso). Other endpoints will evaluate skin-generic quality of life (DLQI-R), Treatment Satisfaction Questionnaire for Medication (TSQM-9), Treatment-related Patient Benefit Index "Standard", 10 items (PBI-S-10), and work productivity and activity impairment (WPAI). Statistical analyses will be based on observed cases. Multiple imputation will be performed as a sensitivity analysis, and adverse events will be reported.

Ethics and dissemination: The study will be conducted according to the protocol, which received ethics committee approval and applicable regulatory requirements of each

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3 participating country. The results will be disseminated through scientific publications and
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5 congress presentations.
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10 **Registration details:** NCT04823247.
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STRENGTHS AND LIMITATIONS OF THIS STUDY

- First clinical study in dermatology using the patient-reported well-being as the primary endpoint in accordance with the holistic definition of health by the World Health Organization (WHO).
- Innovative secondary endpoints such as physician's well-being, patient-defined benefit assessment and the impact of psoriasis on the patients' partner following a people-centred approach claimed by the WHO.
- Relevant sample size from different European countries.
- Patients may experience a biased self-perception due to their inclusion in a clinical study.
- Potential drop-outs or losses to follow-up due to the long observational period.

INTRODUCTION

Psoriasis is an immune-mediated, chronic relapsing inflammatory condition characterised by abnormal differentiation and proliferation of the epidermis affecting skin, nails, and joints [1]. The severity of psoriasis is profound as it includes physical and psychological components [2]. Increasing evidence suggest that psoriasis considerably affects the overall well-being of patients and their families [3], as well as their personal, social, and occupational life [4], often resulting in psychological distress and depression [5–7]. A Europe-wide survey examining quality of life reported that almost 77% of patients believed psoriasis negatively affected normal daily activities and well-being [8]. Moreover, a more recent survey showed that psoriasis patients generally report poor quality of life and physicians are often also not satisfied with their patients' treatment [9]. These studies highlight the need for a well-being evaluation strategy besides the available psoriasis severity scoring assessments [10]. Patient-reported outcomes (PROs) are being used with increasing frequency in clinical trials and provide valuable information on how psoriasis affects physical, social, and psychological aspects of patients' lives. However, the most commonly used decision-making tools in psoriasis, the clinician-reported Psoriasis Area Severity Index (PASI), Physician Global Assessment (PGA) and the patient-reported Dermatology Life Quality Index (DLQI), do not take into account the entire patient disease perspective, leading to misaligned perception between physicians and patients [11]. While the PASI and PGA track changes in psoriasis severity from a clinician's perspective [12,13], the skin-generic DLQI has been used to evaluate psoriasis symptoms and their impact on quality of life [14]. However, the use of the DLQI has been associated with several measurement problems related to age, gender difference, inadequate power to differentiate patients with mild illness, and underestimating patient's emotional status [15,16]. Furthermore, being a sum score and permitting to rate "not relevant" in 8 out of 10 items, DLQI has been shown to provide marked bias and to underestimate the burden of very severely affected

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3 patients[16]. Moreover, a systematic review on skin conditions has highlighted the critical need
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5 for psychiatric assessments in addition to the DLQI score for a full assessment of patient
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patients[16]. Moreover, a systematic review on skin conditions has highlighted the critical need for psychiatric assessments in addition to the DLQI score for a full assessment of patient psychological well-being [17,18].

Unmet needs at the time of biologics

Studies have indicated that a patient-oriented evaluation is critical for overall symptom assessment as physicians' indicators alone cannot capture the disease burden of psoriasis [19–21]. The advent of biologics as monotherapy or in combination with other topical or systemic medications significantly changed the treatment approach for psoriasis representing an advancement over topical treatments or traditional immunosuppressive therapies [22–24]. Biologics target specific components of the immune system and have shown a high benefit-to-risk ratio, high efficacy and acceptable safety profiles [25]. Further, more advanced biologics have been shown to be more cost-effective than first-generation drugs [26,27]. Monoclonal antibodies, selective for the interleukin (IL)-23p19 subunit inhibition, represent a new standard of treatment currently available for the long-term management of psoriasis [28]. Among these, tildrakizumab has demonstrated long-term efficacy and safety in the pivotal phase III studies (reSURFACE 1 and 2) comparing tildrakizumab versus placebo or etanercept for moderate-to-severe psoriasis [29]. However, while biologics are becoming a more important treatment option for individuals with psoriasis, current therapy goals and PROs in dermatology do not fully capture the impact of this therapy on patients' and physicians' well-being [30,31]. Moreover, although several studies have shown that psoriasis significantly affects mental health [32,33], standard severity scores have been found to be very weakly associated with the overall well-being of these patients [34,35]. In practice, there is high need to translate patient burden to patients needs and then derive patient goals conjointly with the patient. Thus, understanding the needs and expectations of patients beyond measuring burden constitutes a fundamental part

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3 of treatment in psoriasis [36]. This is particularly important in sensitive conditions such as nail
4 and anogenital affections [37–39].
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8 **Well-being in psoriasis: clinical goals**

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10 Insights on the well-being of the patients are based on the patient's view of their condition, and
11 this concept is increasingly being embraced as a more comprehensive outcome in line with a
12 holistic view and people-centred perspective, but still undervalued in traditional PROs. Well-
13 being is a holistic multifaceted concept that in a study context describes “to what extent patients
14 will get their healthy lives back”, where mental, physical, and social functioning are
15 interdependent [40]. According to the World Health Organisation (WHO), the ultimate goal of
16 therapy in chronic diseases such as psoriasis is achieving well-being [41]. Nevertheless, well-
17 being has been rarely measured in dermatology so far. A recent study concluded that the DLQI
18 primarily measures physical impairment associated with negative emotions and, thus, provides
19 only a limited evaluation of well-being [42]. Therefore, assessing well-being or specific
20 dimensions of well-being can contribute to a holistic evaluation of patients' health in
21 accordance with the WHO's holistic definition.
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39 **Innovative endpoints in this study**

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41 To assess patient well-being, this study will apply the 5-item WHO Well-being Index (WHO-
42 5), a widely used questionnaire assessing psychological health-related well-being in a variety
43 of chronic diseases such as diabetes, cardiovascular disease, cancer, and depression [43]. For
44 the first time, WHO-5 will be used as a primary endpoint in patients with psoriasis to investigate
45 the improvements that tildrakizumab can achieve on patients' well-being in a real-world setting.
46 Moreover, building a positive cross-talk environment between healthcare professionals and
47 patients is critical. A meta-analysis study including 400 publications reported a higher quality
48 of life and overall improved treatment outcome when patients had higher trust in their physician
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3 [21], underlining how physician's well-being is essential as it can improve patients' satisfaction
4 and interpersonal aspects of care [22]. Patient's behaviour, in turn, can affect physicians' well-
5 being, including unrealistic expectations, aggression, or by developing family-like
6 relationships, resulting in emotional detachment and burnout [23]. As there is no complete
7 correlation between patient- and physician-reported outcome measures, both PROs and
8 physician-reported scores should be considered when assessing treatment outcomes [24]. In this
9 study, the 'Physician's satisfaction' score will be exploited as an innovative tool to investigate
10 the impact of the psoriasis treatment process on physicians' well-being. Furthermore,
11 information on the impact of psoriasis on patients' families, particularly partners, is also
12 lacking, even though the impact of skin disease on family members or partners of patients
13 should be measured while evaluating the burden of psoriasis [3]. Thus, this study will include
14 the questionnaire FamilyPso [44], enabling physicians to better understand the impact of
15 psoriasis as a lifelong chronic disease on partners. This study will provide novel insights into
16 the dimensions of patients' perspectives and their overall state of well-being using a holistic
17 patient-partner and physicians-centred approach. The current study is designed to investigate
18 patient-reported well-being using tildrakizumab in a real-world setting, as well as the impact
19 on their closing environment, including partners and physicians, to provide a more
20 comprehensive overview of people-centred healthcare and their overall state of well-being.
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METHODS AND ANALYSIS

The primary objective is to assess the effect of tildrakizumab on the overall well-being in patients with moderate-to-severe psoriasis using the WHO-5 questionnaire. Secondary objectives include: to evaluate the long-term benefit of tildrakizumab on physician's satisfaction (Physician's Satisfaction Questionnaire) and the impact of psoriasis on patients' partners (FamilyPso questionnaire); to assess the long-term benefit of tildrakizumab reported by patients in terms of skin-generic quality of life (DLQI-R), treatment satisfaction (TSQM-9) and treatment-related benefits (PBI-S-10), work impairment due to psoriasis (WPAI:PSO) and extent of the skin manifestations on the entire body using a "heat map" in a subgroup of patients; to correlate the change of WHO-5 with patients' health-related quality of life (HRQoL) and patients' treatment benefits; to assess the control of skin manifestations (absolute PASI) and its impact on patients, physician's satisfaction and on partners of patients; to describe the socio-demographic and clinical profile of the patients being treated with tildrakizumab, according to the routine clinical practice; and to assess the safety and tolerability of tildrakizumab in a real-world setting. Exploratory objectives are to assess the impact of tildrakizumab on PGA of the skin manifestations and to assess the concordance between patients and physician's satisfaction regarding response to the treatment with tildrakizumab.

Study design

This is an ethics-approved, multi-national, phase IV, 1-cohort prospective observational study planned to be conducted in several countries (Austria, Belgium, France, Germany, Italy, Spain, Switzerland, The Netherlands, and United Kingdom [UK]) to assess patient-reported well-being using tildrakizumab in a live setting. The study design is summarised in **Figure 1**.

Study population

The study population will comprise a minimum of 338 patients with moderate-to-severe plaque psoriasis who need systemic biologic therapy and qualify for treatment with an IL-23p19 inhibitor in real-world clinical practice. Consecutive patients satisfying all the inclusion criteria and none of the exclusion criteria shown in **Table 1** to be eligible for participation will be offered participation. Recruitment will be competitive across all countries participating in the study (i.e., no fixed number of patients per country).

Table 1. Eligibility criteria

Inclusion criteria	
1	Patient with diagnosis of moderate-to-severe chronic plaque psoriasis documented in the medical chart.
2	Patient who needs systemic biologic therapy and qualifies for treatment with an IL-23p19 inhibitor. Tildrakizumab must be the anti-IL-23p19 selected therapy before including the patient in the study.
3	Patient aged 18 years or older at the time of patient recruitment.
4	Patient who has provided written informed consent (if required by country regulations).
Exclusion criteria	
1	Patients unable to comply with the requirements of the study or who, in the opinion of the study physician, should not participate in the study.
2	Patients included in a clinical trial.

IL, interleukin.

Endpoints

Study endpoints cover outcomes reported by patients, their partners, and physicians. The primary endpoint is to assess the overall health-related well-being (evaluated through WHO-5 questionnaire) in patients treated with tildrakizumab according to the marketing authorization and routine clinical practice at the long-term. The secondary endpoints are: physicians' satisfaction evaluation through a composite survey with 16 items (10 generic professional quality of life items and 6 items related to the biological treatment); partner well-being evaluation through the FamilyPso questionnaire; patient's perspective on tildrakizumab long-term benefit evaluation through the (i) skin-generic quality of life questionnaire (DLQI-R), (ii) Treatment Satisfaction Questionnaire for Medication (TSQM-9), (iii) Treatment-related Patient

Benefit Index “Standard”, 10 items (PBI-S-10), (iv) Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI:PSO), (v) skin manifestations distribution (heat map/patient’s grid in a subgroup of patients) according to location and total percentage of area affected, and (vi) the Numeric Rating Scale (NRS) for itch, pain, joint pain, and fatigue assessments; disease control evaluated through the absolute PASI; description of the sociodemographic (age, gender, educational and working status, etc.) and clinical (location of moderate-to-severe psoriasis, comorbid disease, laboratory tests, etc.) characteristics; adverse events (AE) reported during the use of tildrakizumab. The exploratory endpoints are: the control of the skin manifestation evaluation through the PGA; Patient’s and physician’s opinion about tildrakizumab treatment in relation to the therapeutic objectives’ evaluation through the Patient’s and physician’s questionnaire (**Table 2**).

Table 2. Endpoints of the study

	Patient reported outcomes	Partners reported outcomes	Physician reported outcomes	Patient and physician reported outcomes
Primary endpoint	- WHO-5			
Secondary endpoint	- DLQI-R - TSQM-9 - PBI-S-10 - WPAI: PSO - Patient grid - NRS (itch, pain, joint pain, fatigue assessments) - Sociodemographic and clinical characteristics - AEs during tildrakizumab use	- FamilyPso	- Physicians’ satisfaction - Absolute PASI	
Exploratory endpoints			- PGA	- Patient’s and physician’s questionnaire

				- Patient's and physician's satisfaction of being part of the study
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AE, adverse event; DLQI-R, Dermatology Life Quality Index-Revised; NRS, Numeric Rating Scale; PASI, Psoriasis Area Severity Index; PBI-S-10, Patient Benefit Index "Standard", 10 items short form; PGA, Physician Global Assessment; TSQM-9, Treatment Satisfaction Questionnaire for Medication; WHO-5, World Health Organization-Five Well-being Index; WPAI:PSO, Work Productivity and Activity Impairment Questionnaire: Psoriasis.

Data sources and collection

All data will be collected prospectively from the medical charts and entered directly into the electronic data capture system. The study will include both variables extracted from the medical chart and obtained directly from the patients. No visits or examinations, laboratory tests, or procedures are mandated or recommended as part of this study. The data collection schedule is shown in **Table 3**.

Table 3. Data collection schedule

	Baseline visit	Follow-up visit (at 16 and 28 weeks, 12 and 18 months after baseline visit)	Final visit (24 months from baseline)	Early termination visit
Patient characteristics and demographics (including date of ICF signature)	X		X ^a	X ^a
Disease characteristics (diagnosis date, type of psoriasis, severity of psoriasis)	X			
Laboratory test (if it is available)	X	X	X	X
Comorbidities	X	X	X	X
Concomitant medication	X	X	X	X
Drug therapy history	X			
Tildrakizumab drug therapy (dose)	X	X	X	X
PASI	X	X	X	X

	Baseline visit	Follow-up visit (at 16 and 28 weeks, 12 and 18 months after baseline visit)	Final visit (24 months from baseline)	Early termination visit
Heat map/patient's grid (subgroup of patients): location of skin manifestations	X	X	X	X
Adverse event reporting	X	X	X	X
Questionnaires				
WHO-5	X	X	X	X
DLQI-R	X	X	X	X
PBI-S-10	X	X	X	X
TSQM-9	X	X	X	X
WPAI:PSO	X	X	X	X
FamilyPso	X	X	X	X
NRS (itch, pain, joint pain, fatigue)	X	X	X	X
Patient's and Physician's satisfaction of being part in the study (open field question)	X		X	X
PGA	X	X	X	X
Physician's satisfaction	X	X	X	X
Patient's and physician's questionnaire		X	X	X

DLQI-R, Dermatology Life Quality Index-Revised; ICF, informed consent form; NRS, Numeric Rating Scale; PASI, Psoriasis Area Severity Index; PBI-S-10, Patient Benefit Index "Standard", 10 items short form; PGA, Physician Global Assessment; TSQM-9, Treatment Satisfaction Questionnaire for Medication ;WHO-5, World Health Organization-Five Well-being Index; WPAI:PSO, Work Productivity and Activity Impairment Questionnaire: Psoriasis; a, Variables such as gender or height will not be collected at these visits .

Questionnaires

All the questionnaires included in the study have validated translations according to international guidelines from the original language to the official languages in the participating countries.

Primary endpoint:

1. The 5-item World Health Organization Well-being Index (WHO-5): The WHO-5 is a generic global rating scale measuring subjective well-being containing positive statements. The respondent is asked to rate how well each of the 5 items applies to him

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3 or her when considering the last 14 days. Each of the 5 items is scored from 5 (all of the
4 time) to 0 (none of the time). The raw score therefore theoretically ranges from 0
5 (absence of well-being) to 25 (maximal well-being). To standardize the score on a scale
6 from 0 (absent) to 100 (maximal), it is recommended to multiply the raw score by 4
7 [43].
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14 **Secondary endpoints:**

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17 2. Dermatology Life Quality Index-Relevant (DLQI-R): The DLQI-R is a recently
18 developed scoring that adjusts the total score of the questionnaire for the number of 'not
19 relevant' responses indicated by a patient. It is a self-administrated questionnaire
20 validated as a dermatology-specific quality of life instrument. It includes 10 items to
21 assess patient's HRQoL during the previous week on a 4-point scale, indicating 'not at
22 all', 'a little', 'a lot' and 'very much', respectively. For each patient, the DLQI-R score
23 is estimated as a sum score of the original DLQI score replacing items rated "not
24 relevant" by the mean of the other items [45].
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26 3. Patient Benefit Index "Standard", 10-item short form (PBI-S-10: 10 items describing
27 treatment goals of patients with skin diseases. Before treatment, these goals are rated on
28 a 5-point Likert-scale (0="not at all", 4="very") according to their perceived relevance
29 (PNQ). Alternatively, patients can state that a goal "does not apply" to them. In the
30 course of treatment, patients are asked to express the achievement of these 10 treatment
31 goals (treatment benefit) on the same 5-point Likert-scale (PBQ), again with the
32 opportunity to state that the goal did not apply [46]. An overall index of patient benefits
33 (PBI) is calculated by adding the single weighted benefits to a sum score reaching from
34 0=no patient benefit to 4=very strong patient benefit.
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36 4. Treatment Satisfaction Questionnaire for Medication (TSQM-9): It is a self-
37 administrated questionnaire that measures patients' drug therapy satisfaction
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3 considering the last two or three weeks or since the last time the patient took the
4 medication. It consists of 9 statements distributed in 3 domains: efficacy (3 items),
5 convenience (3 items) and global satisfaction (3 items). Responses are measured on a
6 Likert scale of 5 or 7 points [47,48].
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12 5. Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI: PSO): It
13 is a self-administrated questionnaire that measures the impact on the work productivity
14 in patients with psoriasis considering the last seven days. The questionnaire contains 6
15 items with dichotomous response options [49].
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- 21 6. Numeric Rating Scale (NRS) (itch, pain, joint pain, fatigue): It is a self-administrated
22 questionnaire to assess patients' itch severity, pain, joint pain and fatigue. The
23 questionnaire has a single-item that describes the worst level of itching, joint pain and
24 fatigue, respectively, due to psoriasis in the past 24 hours [50].
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- 30 7. FamilyPso: It is a self-administrated questionnaire to assess the burden on partners of
31 patients with psoriasis. The questionnaire has 15 items divided in 5 factors: 1) Perceived
32 strain by social reactions to the partner's psoriasis; 2) Strain caused by cleaning; 3)
33 Acute emotional strain attributed directly to the psoriasis; 4) Restrictions of social life;
34 5) General emotional strain. The items are scaled in a 5-point Likert format: 0='not
35 true', 1='somewhat true', 2='moderately true', 3='quite true', 4='very true', with the
36 supplementary option 'does not apply to me' [44].
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- 47 8. Patient's and physician's questionnaire: Survey of 10 questions elaborated for this
48 project with the objective to assess the opinion of physicians and patients about
49 tildrakizumab treatment in relation to the therapeutic objectives. The physician will
50 respond according to his/her assessment in relation to the response to tildrakizumab
51 treatment of each patient. Each item is scaled in a 5-points Likert format: 'strongly
52 agree', 'agree', 'uncertain', 'disagree' and 'strongly disagree'.
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3 9. Psoriasis Area and Severity Index (PASI): measure of psoriasis severity average to
4 quantify psoriasis grade [51], combining an assessment of each psoriasis lesion graded
5 on a 0-4 scale (0=none and 4=maximum) based on three parameters of the lesions
6 including, erythema (redness), induration (thickness), desquamation (scaliness) and on
7 a weighted evaluation of the affected area (from 0=affecting 0% to 6=affecting 100%),
8 dividing the body into four sections: head (10% of person's skin), trunk (30%), upper
9 extremities (20%) and lower extremities (40%). Each area is scored by itself.
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19 10. Physician Global Assessment (PGA): A 5-point ordinal scale used to assess the severity
20 of disease over the body including global, scalp, palmoplantar and nails. The scale
21 ranges from 0 to 4 for global, scalp and palmoplantar assessment [52]:
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26 0= clear: no signs of psoriasis

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28 1= almost clear: only minimal plaque elevation, scaling, and/or erythema

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30 2= mild: slight plaque elevation, scaling, and/or erythema

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32 3= moderate: moderate plaque elevation, scaling, and/or erythema

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34 4= severe: very marked plaque elevation, scaling, and/or erythema
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37 For nails assessment, the scale ranges from 0 to 4:
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40 0= none: normal nail appearance

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42 1= mild: pitting and/or oil drops; mild disfigurement

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44 2= moderate: prominent visible pitting and/or oil drops, distal onycholysis
45 with/without hyperkeratosis; moderate disfigurement
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49 3= severe: pronounced nail changes including pitting, oil drops, distal
50 onycholysis with/without hyperkeratosis, onychodystrophy; substantial
51 disfigurement
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55 4= very severe: severe distal onycholysis with/without hyperkeratosis and/or
56 severe onychodystrophy; prominent disfigurement
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3 11. Physician's satisfaction: A composite survey with 16 items, 10 of them are generic
4 items and correspond to the compassion subscale of the Professional Quality of Life
5 questionnaire [53]; and 6 items were specifically created for this study regarding
6 biological treatment. There are 5-point scales that reflect how frequently the physician
7 experienced this thing in the last 30 days.
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14 12. Patient's and physician's satisfaction of being part of the study: open question to assess
15 the satisfaction that the participation on a clinical study may provide to the patients and
16 physicians.
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22 **Sample size calculation**

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24 A total sample size of 338 patients with baseline WHO-5 score ≤ 50 will provide a 95% power
25 to detect a difference of 10 points [43] in the absolute change from baseline in the WHO-5 total
26 score at week 24, assuming 50.5 as the standard deviation of the difference. This sample size
27 of 338 patients produces a two-sided 95% confidence interval with a precision of ± 5.4 points.
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30 A conservative estimation assumes that 75% of the psoriatic population may have a baseline
31 WHO-5 score ≤ 50 [54]. Therefore, around 450 patients will have to be included in the study to
32 ensure the 338 patients previously described. Also considering a 10% drop out rate, the final
33 number of patients to be included will be approximately 500.
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44 **Data analyses and reporting**

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46 All data analyses will be performed using SAS[®] version 9.2 or higher (SAS Institute, Cary, NC,
47 USA). Descriptive analyses will be performed. Statistical analyses will be based on observed
48 cases. Multiple imputation will be performed as a sensitivity analysis. All AE verbatim terms
49 will be coded using the Medical Dictionary for Regulatory Activities. Medication will be coded
50 using WHO Drug Dictionary. Final analyses will be performed once the data from all patients
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3 have been collected in the database, cleaned, and database lock has occurred. Analyses will be
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5 performed overall and per country.
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8 Changes in WHO-5 (to assess the primary objective) and changes in DLQI-R, PBI-S-10,
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10 TSQM-9, patient's and physician's, and NRS scores will be calculated as the difference
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12 between baseline and follow-up visits (up to 24 months) and will be compared using paired t-
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14 test (or Wilcoxon signed-rank test). Furthermore, all answers will be described by number of
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16 patients who answer in each category or domain (if applicable). To assess the "correlation of
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18 the change of health-related well-being (WHO-5)", a Pearson product-moment correlation
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20 coefficient (r) will be used and, for ordinal data, a Spearman's rank-order correlation will be
21
22 used. Work and activity impairment will be analysed using the responses to the WPAI:PSO
23
24 questionnaire in patients actively working in the last 7 days. Activity impairment will be
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26 calculated in each study visit. Changes in WPAI:PSO scores will be calculated as the difference
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28 between baseline and follow-up visits (up to 24 months) and will be compared using paired t-
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30 test (or Wilcoxon signed-rank test). FamilyPso questionnaire will be described through each
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32 factor and for total score. For additional outcomes, PASI values will be correlated with the
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34 different clinical questionnaires thorough Pearson correlation (r) in order to assess positive
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36 impact of the control of skin manifestations.
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44 **Patient and public involvement statement**

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46 Patients or the public were not involved in the design of the study, and will not be involved in
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48 the conduct, reporting, or dissemination plans of this research.
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ETHICS AND DISSEMINATION

This non-interventional study will be conducted in compliance with the protocol, all applicable regulatory requirements of the countries where the study is being conducted and the ethical principles of the latest version of the Declaration of Helsinki that are consistent with Good Pharmacoepidemiology Practices. Data protection and privacy regulations will be strictly observed in capturing, forwarding, processing, and storing patient data according to the Directive 95/46/EC on the protection of individuals and in compliance with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). The protocol has been approved by the following ethics committees: (i) Medizinische Universität Graz - Ethikkommission (Austria, reference number: 33-555 ex 20/21), (ii) Comité d’Ethique hospitalo-facultaire (CEHF) Cliniques universitaires Saint-Luc (Belgium, reference number BC-10914), (iii) Comité de Protection des Personnes Nord-Ouest III (France, reference number: 2021-61), (iv) Medizinische Fakultät der Christian-Albrechts-Universität zu Kiel - Ethik Kommission (Germany, reference number: D 480/21), (v) Comitato Etico Università Federico II (Italy, reference number: 295/21), (vi) CEIC Aragón (CEICA) (Spain, reference number: EPA21/016, Acta 11/2021), (vii) Ethikkommission Nordwest- und Zentralschweiz (EKNZ) (Switzerland, reference number: 2021-01705), (viii) DCRF/NWMO Advisory Commission UMC Groningen (The Netherlands, reference number: NWMO 21.09.035), and (ix) London - Hampstead Research Ethics Committee (UK, reference number: 21/PR/0883).

The results of the POSITIVE study will be disseminated through one or more scientific manuscripts and may also be presented at medical congresses.

DISCUSSION

The lack of patient-oriented outcome measures for assessing the overall well-being of patients with psoriasis is becoming a concern in dermatology clinical practice and research. Psoriasis heavily affects the physical, psychological and social well-being of patients and that of their family members and partners, thus, beside clinical assessments, the full impact of psoriasis treatment on the patient and people around should be recognised. To our knowledge, the POSITIVE study is the first study to apply the WHO-5 as a primary endpoint to estimate the improvements on patients' well-being treated with tildrakizumab in a real-world setting. This study will measure the well-being of patients, their partners and of physicians, for a better understanding of the impact of psoriasis as a chronic disease on patients' and their close environment. The results of this study could potentially be added to the available psoriasis evaluation methods and provide dermatologists with new tools to improve their own and patient's well-being enhancing patient-clinician relationships. The need to provide results from the POSITIVE study becomes essential given the WHO claim for people-centred healthcare and patient commitment. The POSITIVE study will significantly promote patients' involvement and awareness as recommended by the WHO global report on psoriasis [5], as the most common root for patient dissatisfaction is being poorly engaged in the treatment decision-making process. Limitations of the study will include potential bias and missing information or possible drop-outs or lost to follow-up in the last follow-up visits of the study because of the long observational period. In addition, potential time-related maturation/history effects on the primary outcome measure of general well-being should be considered, especially post-pandemic, given the long observational period and the lack of a control group. Moreover, patients included in this study will have to be preselected to initiate tildrakizumab therapy before patient inclusion in the study. Finally, a limitation could be represented by patient-related bias on self-perception due to the inclusion in a clinical study.

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3 In summary, this prospective observation study constitutes an innovative people-centric
4 approach to investigate how intervention with tildrakizumab may improve the well-being of
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6 patients, their families, and healthcare professionals.
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For peer review only

ETHICS STATEMENT

Patient consent for publication

Not required.

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MA, RS, ED, PL, EdJ, GF, LN, AN, JL, ZR, SG, EM, TO, IK, and UM were involved in conception and study design. **MA, RS, ED, PL, EdJ, GF, LN, AN, JL, ZR, SG, EM, TO, IK, and UM** provided edits, critiqued the manuscript for intellectual content, and approved the final manuscript.

COMPETING INTERESTS

MA has served as consultant for, or has been a paid speaker for clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including Abbvie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Eli-Lilly, GSK, Janssen-Cilag, Leo Pharma, Medac, Merck, MSD, Novartis, Pfizer, UCB, and Xenoport; **RS** has been an advisor and/or received speaker honoraria and/or received grants from AbbVie, Almirall, Beiersdorf, Janssen, LEO Pharma and Novartis; **ED** has the following conflict of interests: Advisory Board member, consultant, grants, research support, participation in clinical trials, honorarium for speaking, research support, with the following pharmaceutical companies: Abbvie/Abbott, Almirall, Amgen, Janssen-Cilag, Leo Pharma, Novartis, Pfizer, MSD-Schering-Plough, Celgene, Lilly, and UCB; **PL** received honoraria and/or grants as an investigator, speaker, and/or advisory board member for AbbVie, Almirall, Actelion, Celgene, Janssen, Lilly, Sanofi, Leo, UCB, and Novartis; **EdJ** has received research grants for the independent research fund of the department of dermatology of the Radboud University

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17 consultant for AbbVie, Almirall, Eli Lilly, Leo Pharma, Janssen, Novartis, and UCB; **LN**
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3 and/or received speakers' honoraria and/or received grants and/or participated in clinical trials
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5 of the following companies: AbbVie, Aditxt, Almirall, Amgen, Aristeia, Boehringer-Ingelheim,
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21 Not applicable.
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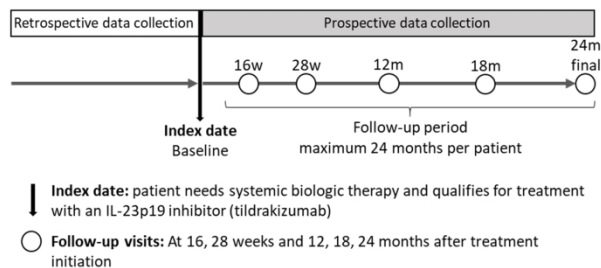
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3 **FIGURE LEGENDS**
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5 **Figure 1.** Study design of the POSITIVE study
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BMJ Open

PATIENT-REPORTED WELL-BEING IN VALUE-BASED CARE USING TILDRAKIZUMAB IN A REAL WORLD SETTING: PROTOCOL OF A MULTI-NATIONAL, PHASE IV, 1 COHORT PROSPECTIVE OBSERVATIONAL STUDY (THE POSITIVE STUDY)

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3 **PATIENT-REPORTED WELL-BEING IN VALUE-BASED CARE USING**
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7 **NATIONAL, PHASE IV, 1-COHORT PROSPECTIVE OBSERVATIONAL STUDY**
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9 **(THE POSITIVE STUDY)**
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ABSTRACT

Introduction: Psoriasis is a chronic inflammatory skin disease that negatively impacts the quality of life of patients and their families. However, the most commonly used decision-making tools in psoriasis, Psoriasis Area and Severity Index (PASI), Physician Global Assessment (PGA) and Dermatology Life Quality Index (DLQI), do not fully capture the impact of psoriasis on patients' lives. In contrast, the well-established 5-item World Health Organization Well-being Index (WHO-5) assesses the subjective psychological well-being of patients. Moreover, while drug innovations became available for psoriasis, data on the impact of these therapies on patients' lives and their closest environment (family, physicians) is limited. This study will assess the effect of tildrakizumab, an interleukin-23p19 inhibitor, on the overall well-being of patients with moderate-to-severe psoriasis. Moreover, the long-term benefit of tildrakizumab on physicians' satisfaction and psoriasis patients' partners' lives will be evaluated.

Methods and analysis: This non-interventional, prospective, observational, real-world evidence study will involve multiple sites in Europe and approximately 500 adults with moderate-to-severe psoriasis treated with tildrakizumab. Each patient will be followed for 24 months. The primary endpoint is well-being measured by the WHO-5 questionnaire. Key secondary endpoints include Physician's Satisfaction and partner's quality of life (FamilyPso). Other endpoints will evaluate skin-generic quality of life (DLQI-R), Treatment Satisfaction Questionnaire for Medication (TSQM-9), Treatment-related Patient Benefit Index "Standard", 10 items (PBI-S-10), and work productivity and activity impairment (WPAI). Statistical analyses will be based on observed cases. Multiple imputation will be performed as a sensitivity analysis, and adverse events will be reported.

Ethics and dissemination: The study will be conducted according to the protocol, which received ethics committee approval and applicable regulatory requirements of each

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3 participating country. The results will be disseminated through scientific publications and
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5 congress presentations.
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10 **Registration details:** NCT04823247.
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STRENGTHS AND LIMITATIONS OF THIS STUDY

- First clinical study in dermatology using the patient-reported well-being as the primary endpoint in accordance with the holistic definition of health by the World Health Organization (WHO).
- Innovative secondary endpoints such as physician's well-being, patient-defined benefit assessment and patients' partner well-being, following a people-centred approach claimed by the WHO, for a better understanding of the impact of a chronic disease such as psoriasis both on patients and their close environment.
- Relevant sample size.
- Patients may experience a biased self-perception of well-being due to their inclusion in a clinical study.
- Potential drop-outs or losses to follow-up due to the long observational period.

INTRODUCTION

Psoriasis is an immune-mediated, chronic relapsing inflammatory condition characterised by abnormal differentiation and proliferation of the epidermis affecting skin, nails, and joints [1]. The severity of psoriasis is profound as it includes physical and psychological components [2]. Increasing evidence suggest that psoriasis considerably affects the overall well-being of patients and their families [3], as well as their personal, social, and occupational life [4], often resulting in psychological distress and depression [5–7]. A Europe-wide survey examining quality of life reported that almost 77% of patients believed psoriasis negatively affected normal daily activities and well-being [8]. Moreover, a more recent survey showed that psoriasis patients generally report poor quality of life and physicians are often also not satisfied with their patients' treatment [9]. These studies highlight the need for a well-being evaluation strategy besides the available psoriasis severity scoring assessments [10]. Patient-reported outcomes (PROs) are being used with increasing frequency in clinical trials and provide valuable information on how psoriasis affects physical, social, and psychological aspects of patients' lives. However, the most commonly used decision-making tools in psoriasis, the clinician-reported Psoriasis Area Severity Index (PASI), Physician Global Assessment (PGA) and the patient-reported Dermatology Life Quality Index (DLQI), do not take into account the entire patient disease perspective, leading to misaligned perception between physicians and patients [11]. While the PASI and PGA track changes in psoriasis severity from a clinician's perspective [12,13], the skin-generic DLQI has been used to evaluate psoriasis symptoms and their impact on quality of life [14]. However, the use of the DLQI has been associated with several measurement problems related to age, gender difference, inadequate power to differentiate patients with mild illness, and underestimating patient's emotional status [15,16]. Furthermore, being a sum score and permitting to rate "not relevant" in 8 out of 10 items, DLQI has been shown to provide marked bias and to underestimate the burden of very severely affected

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3 patients[16]. Moreover, a systematic review on skin conditions has highlighted the critical need
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5 for psychiatric assessments in addition to the DLQI score for a full assessment of patient
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patients[16]. Moreover, a systematic review on skin conditions has highlighted the critical need for psychiatric assessments in addition to the DLQI score for a full assessment of patient psychological well-being [17,18].

Unmet needs at the time of biologics

Studies have indicated that a patient-oriented evaluation is critical for overall symptom assessment as physicians' indicators alone cannot capture the disease burden of psoriasis [19–21]. The advent of biologics as monotherapy or in combination with other topical or systemic medications significantly changed the treatment approach for psoriasis representing an advancement over topical treatments or traditional immunosuppressive therapies [22–24]. Biologics target specific components of the immune system and have shown a high benefit-to-risk ratio, high efficacy and acceptable safety profiles [25]. Further, more advanced biologics have been shown to be more cost-effective than first-generation drugs [26,27]. Monoclonal antibodies, selective for the interleukin (IL)-23p19 subunit inhibition, represent a new standard of treatment currently available for the long-term management of psoriasis [28]. Among these, tildrakizumab has demonstrated long-term efficacy and safety in the pivotal phase III studies (reSURFACE 1 and 2) comparing tildrakizumab versus placebo or etanercept for moderate-to-severe psoriasis [29]. However, while biologics are becoming a more important treatment option for individuals with psoriasis, current therapy goals and PROs in dermatology do not fully capture the impact of this therapy on patients' and physicians' well-being [30,31]. Moreover, although several studies have shown that psoriasis significantly affects mental health [32,33], standard severity scores have been found to be very weakly associated with the overall well-being of these patients [34,35]. In practice, there is high need to translate patient burden to patients needs and then derive patient goals conjointly with the patient. Thus, understanding the needs and expectations of patients beyond measuring burden constitutes a fundamental part

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3 of treatment in psoriasis [36]. This is particularly important in sensitive conditions such as nail
4 and anogenital affections [37–39].
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8 **Well-being in psoriasis: clinical goals**

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10 Insights on the well-being of the patients are based on the patient’s view of their condition, and
11 this concept is increasingly being embraced as a more comprehensive outcome in line with a
12 holistic view and people-centred perspective, but still undervalued in traditional PROs. Well-
13 being is a holistic multifaceted concept that in a study context describes “to what extent patients
14 will get their healthy lives back”, where mental, physical, and social functioning are
15 interdependent [40]. According to the World Health Organisation (WHO), the ultimate goal of
16 therapy in chronic diseases such as psoriasis is achieving well-being [41]. Nevertheless, well-
17 being has been rarely measured in dermatology so far. A recent study concluded that the DLQI
18 primarily measures physical impairment associated with negative emotions and, thus, provides
19 only a limited evaluation of well-being [42]. Therefore, assessing well-being or specific
20 dimensions of well-being can contribute to a holistic evaluation of patients’ health in
21 accordance with the WHO’s holistic definition.
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39 **Innovative endpoints in this study**

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41 To assess patient well-being, this study will apply the 5-item WHO Well-being Index (WHO-
42 5), a widely used questionnaire assessing psychological health-related well-being in a variety
43 of chronic diseases such as diabetes, cardiovascular disease, cancer, and depression [43]. For
44 the first time, WHO-5 will be used as a primary endpoint in patients with psoriasis to investigate
45 the improvements that tildrakizumab can achieve on patients’ well-being in a real-world setting.
46 Moreover, building a positive cross-talk environment between healthcare professionals and
47 patients is critical. A meta-analysis study including 400 publications reported a higher quality
48 of life and overall improved treatment outcome when patients had higher trust in their physician
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3 [21], underlining how physician's well-being is essential as it can improve patients' satisfaction
4 and interpersonal aspects of care [22]. Patient's behaviour, in turn, can affect physicians' well-
5 being, including unrealistic expectations, aggression, or by developing family-like
6 relationships, resulting in emotional detachment and burnout [23]. As there is no complete
7 correlation between patient- and physician-reported outcome measures, both PROs and
8 physician-reported scores should be considered when assessing treatment outcomes [24]. In this
9 study, the 'Physician's satisfaction' score will be exploited as an innovative tool to investigate
10 the impact of the psoriasis treatment process on physicians' well-being. Furthermore,
11 information on the impact of psoriasis on patients' families, particularly partners, is also
12 lacking, even though the impact of skin disease on family members or partners of patients
13 should be measured while evaluating the burden of psoriasis [3]. Thus, this study will include
14 the questionnaire FamilyPso [44], enabling physicians to better understand the impact of
15 psoriasis as a lifelong chronic disease on partners. This study will provide novel insights into
16 the dimensions of patients' perspectives and their overall state of well-being using a holistic
17 patient-partner and physicians-centred approach. The current study is designed to investigate
18 patient-reported well-being using tildrakizumab in a real-world setting, as well as the impact
19 on their closing environment, including partners and physicians, to provide a more
20 comprehensive overview of people-centred healthcare and their overall state of well-being.
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METHODS AND ANALYSIS

The primary objective is to assess the effect of tildrakizumab on the overall well-being in patients with moderate-to-severe psoriasis using the WHO-5 questionnaire. Secondary objectives include: to evaluate the long-term benefit of tildrakizumab on physician's satisfaction (Physician's Satisfaction Questionnaire) and the impact of psoriasis on patients' partners (FamilyPso questionnaire); to assess the long-term benefit of tildrakizumab reported by patients in terms of skin-generic quality of life (DLQI-R), treatment satisfaction (TSQM-9) and treatment-related benefits (PBI-S-10), work impairment due to psoriasis (WPAI:PSO) and extent of the skin manifestations on the entire body using a "heat map" in a subgroup of patients; to correlate the change of WHO-5 with patients' health-related quality of life (HRQoL) and patients' treatment benefits; to assess the control of skin manifestations (absolute PASI) and its impact on patients, physician's satisfaction and on partners of patients; to describe the socio-demographic and clinical profile of the patients being treated with tildrakizumab, according to the routine clinical practice; and to assess the safety and tolerability of tildrakizumab in a real-world setting. Exploratory objectives are to assess the impact of tildrakizumab on PGA of the skin manifestations and to assess the concordance between patients and physician's satisfaction regarding response to the treatment with tildrakizumab.

Study design

This is an ethics-approved, multi-national, phase IV, 1-cohort prospective observational study planned to be conducted in several countries (Austria, Belgium, France, Germany, Italy, Spain, Switzerland, The Netherlands, and United Kingdom [UK]) to assess patient-reported well-being using tildrakizumab in a live setting. The study design is summarised in **Figure 1**.

Study population

The study population will comprise a minimum of 338 patients with moderate-to-severe plaque psoriasis who need systemic biologic therapy and qualify for treatment with an IL-23p19 inhibitor in real-world clinical practice. Consecutive patients satisfying all the inclusion criteria and none of the exclusion criteria shown in **Table 1** to be eligible for participation will be offered participation. Recruitment will be competitive across all countries participating in the study (i.e., no fixed number of patients per country).

Table 1. Eligibility criteria

Inclusion criteria	
1	Patient with diagnosis of moderate-to-severe chronic plaque psoriasis documented in the medical chart.
2	Patient who needs systemic biologic therapy and qualifies for treatment with an IL-23p19 inhibitor. Tildrakizumab must be the anti-IL-23p19 selected therapy before including the patient in the study.
3	Patient aged 18 years or older at the time of patient recruitment.
4	Patient who has provided written informed consent (if required by country regulations).
Exclusion criteria	
1	Patients unable to comply with the requirements of the study or who, in the opinion of the study physician, should not participate in the study.
2	Patients included in a clinical trial.

IL, interleukin.

Endpoints

Study endpoints cover outcomes reported by patients, their partners, and physicians. The primary endpoint is to assess the overall health-related well-being (evaluated through WHO-5 questionnaire) in patients treated with tildrakizumab according to the marketing authorization and routine clinical practice at the long-term. The secondary endpoints are: physicians' satisfaction evaluation through a composite survey with 16 items (10 generic professional quality of life items and 6 items related to the biological treatment); partner well-being evaluation through the FamilyPso questionnaire; patient's perspective on tildrakizumab long-term benefit evaluation through the (i) skin-generic quality of life questionnaire (DLQI-R), (ii) Treatment Satisfaction Questionnaire for Medication (TSQM-9), (iii) Treatment-related Patient

Benefit Index “Standard”, 10 items (PBI-S-10), (iv) Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI:PSO), (v) skin manifestations distribution (heat map/patient’s grid in a subgroup of patients) according to location and total percentage of area affected, and (vi) the Numeric Rating Scale (NRS) for itch, pain, joint pain, and fatigue assessments; disease control evaluated through the absolute PASI; description of the sociodemographic (age, gender, educational and working status, etc.) and clinical (location of moderate-to-severe psoriasis, comorbid disease, laboratory tests, etc.) characteristics; adverse events (AE) reported during the use of tildrakizumab. The exploratory endpoints are: the control of the skin manifestation evaluation through the PGA; Patient’s and physician’s opinion about tildrakizumab treatment in relation to the therapeutic objectives’ evaluation through the Patient’s and physician’s questionnaire (**Table 2**).

Table 2. Endpoints of the study

	Patient reported outcomes	Partners reported outcomes	Physician reported outcomes	Patient and physician reported outcomes
Primary endpoint	- WHO-5			
Secondary endpoint	- DLQI-R - TSQM-9 - PBI-S-10 - WPAI: PSO - Patient grid - NRS (itch, pain, joint pain, fatigue assessments) - Sociodemographic and clinical characteristics - AEs during tildrakizumab use	- FamilyPso	- Physicians’ satisfaction - Absolute PASI	
Exploratory endpoints			- PGA	- Patient’s and physician’s questionnaire

				- Patient's and physician's satisfaction of being part of the study
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AE, adverse event; DLQI-R, Dermatology Life Quality Index-Revised; NRS, Numeric Rating Scale; PASI, Psoriasis Area Severity Index; PBI-S-10, Patient Benefit Index "Standard", 10 items short form; PGA, Physician Global Assessment; TSQM-9, Treatment Satisfaction Questionnaire for Medication; WHO-5, World Health Organization-Five Well-being Index; WPAI:PSO, Work Productivity and Activity Impairment Questionnaire: Psoriasis.

Data sources and collection

All data will be collected prospectively from the medical charts and entered directly into the electronic data capture system. The study will include both variables extracted from the medical chart and obtained directly from the patients. No visits or examinations, laboratory tests, or procedures are mandated or recommended as part of this study. The data collection schedule is shown in **Table 3**.

Table 3. Data collection schedule

	Baseline visit	Follow-up visit (at 16 and 28 weeks, 12 and 18 months after baseline visit)	Final visit (24 months from baseline)	Early termination visit
Patient characteristics and demographics (including date of ICF signature)	X		X ^a	X ^a
Disease characteristics (diagnosis date, type of psoriasis, severity of psoriasis)	X			
Laboratory test (if it is available)	X	X	X	X
Comorbidities	X	X	X	X
Concomitant medication	X	X	X	X
Drug therapy history	X			
Tildrakizumab drug therapy (dose)	X	X	X	X
PASI	X	X	X	X

	Baseline visit	Follow-up visit (at 16 and 28 weeks, 12 and 18 months after baseline visit)	Final visit (24 months from baseline)	Early termination visit
Heat map/patient's grid (subgroup of patients): location of skin manifestations	X	X	X	X
Adverse event reporting	X	X	X	X
Questionnaires				
WHO-5	X	X	X	X
DLQI-R	X	X	X	X
PBI-S-10	X	X	X	X
TSQM-9	X	X	X	X
WPAI:PSO	X	X	X	X
FamilyPso	X	X	X	X
NRS (itch, pain, joint pain, fatigue)	X	X	X	X
Patient's and Physician's satisfaction of being part in the study (open field question)	X		X	X
PGA	X	X	X	X
Physician's satisfaction	X	X	X	X
Patient's and physician's questionnaire		X	X	X

DLQI-R, Dermatology Life Quality Index-Revised; ICF, informed consent form; NRS, Numeric Rating Scale; PASI, Psoriasis Area Severity Index; PBI-S-10, Patient Benefit Index "Standard", 10 items short form; PGA, Physician Global Assessment; TSQM-9, Treatment Satisfaction Questionnaire for Medication ;WHO-5, World Health Organization-Five Well-being Index; WPAI:PSO, Work Productivity and Activity Impairment Questionnaire: Psoriasis; a, Variables such as gender or height will not be collected at these visits.

Questionnaires

All the questionnaires included in the study have validated translations according to international guidelines from the original language to the official languages in the participating countries.

Primary endpoint:

1. The 5-item World Health Organization Well-being Index (WHO-5): The WHO-5 is a generic global rating scale measuring subjective well-being containing positive statements. The respondent is asked to rate how well each of the 5 items applies to him

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3 or her when considering the last 14 days. Each of the 5 items is scored from 5 (all of the
4 time) to 0 (none of the time). The raw score therefore theoretically ranges from 0
5 (absence of well-being) to 25 (maximal well-being). To standardize the score on a scale
6 from 0 (absent) to 100 (maximal), it is recommended to multiply the raw score by 4
7 [43].
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14 **Secondary endpoints:**

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- 17 2. Dermatology Life Quality Index-Relevant (DLQI-R): The DLQI-R is a recently
18 developed scoring that adjusts the total score of the questionnaire for the number of 'not
19 relevant' responses indicated by a patient. It is a self-administrated questionnaire
20 validated as a dermatology-specific quality of life instrument. It includes 10 items to
21 assess patient's HRQoL during the previous week on a 4-point scale, indicating 'not at
22 all', 'a little', 'a lot' and 'very much', respectively. For each patient, the DLQI-R score
23 is estimated as a sum score of the original DLQI score replacing items rated "not
24 relevant" by the mean of the other items [45].
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 - 27 3. Patient Benefit Index "Standard", 10-item short form (PBI-S-10: 10 items describing
28 treatment goals of patients with skin diseases. Before treatment, these goals are rated on
29 a 5-point Likert-scale (0="not at all", 4="very") according to their perceived relevance
30 (PNQ). Alternatively, patients can state that a goal "does not apply" to them. In the
31 course of treatment, patients are asked to express the achievement of these 10 treatment
32 goals (treatment benefit) on the same 5-point Likert-scale (PBQ), again with the
33 opportunity to state that the goal did not apply [46]. An overall index of patient benefits
34 (PBI) is calculated by adding the single weighted benefits to a sum score reaching from
35 0=no patient benefit to 4=very strong patient benefit.
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 - 38 4. Treatment Satisfaction Questionnaire for Medication (TSQM-9): It is a self-
39 administrated questionnaire that measures patients' drug therapy satisfaction
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3 considering the last two or three weeks or since the last time the patient took the
4 medication. It consists of 9 statements distributed in 3 domains: efficacy (3 items),
5 convenience (3 items) and global satisfaction (3 items). Responses are measured on a
6 Likert scale of 5 or 7 points [47,48].
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12 5. Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI: PSO): It
13 is a self-administrated questionnaire that measures the impact on the work productivity
14 in patients with psoriasis considering the last seven days. The questionnaire contains 6
15 items with dichotomous response options [49].
16
17 6. Numeric Rating Scale (NRS) (itch, pain, joint pain, fatigue): It is a self-administrated
18 questionnaire to assess patients' itch severity, pain, joint pain and fatigue. The
19 questionnaire has a single-item that describes the worst level of itching, joint pain and
20 fatigue, respectively, due to psoriasis in the past 24 hours [50].
21
22 7. FamilyPso: It is a self-administrated questionnaire to assess the burden on partners of
23 patients with psoriasis. The questionnaire has 15 items divided in 5 factors: 1) Perceived
24 strain by social reactions to the partner's psoriasis; 2) Strain caused by cleaning; 3)
25 Acute emotional strain attributed directly to the psoriasis; 4) Restrictions of social life;
26 5) General emotional strain. The items are scaled in a 5-point Likert format: 0='not
27 true', 1='somewhat true', 2='moderately true', 3='quite true', 4='very true', with the
28 supplementary option 'does not apply to me' [44].
29
30 8. Patient's and physician's questionnaire: Survey of 10 questions elaborated for this
31 project with the objective to assess the opinion of physicians and patients about
32 tildrakizumab treatment in relation to the therapeutic objectives. The physician will
33 respond according to his/her assessment in relation to the response to tildrakizumab
34 treatment of each patient. Each item is scaled in a 5-points Likert format: 'strongly
35 agree', 'agree', 'uncertain', 'disagree' and 'strongly disagree'.
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3 9. Psoriasis Area and Severity Index (PASI): measure of psoriasis severity average to
4 quantify psoriasis grade [51], combining an assessment of each psoriasis lesion graded
5 on a 0-4 scale (0=none and 4=maximum) based on three parameters of the lesions
6 including, erythema (redness), induration (thickness), desquamation (scaliness) and on
7 a weighted evaluation of the affected area (from 0=affecting 0% to 6=affecting 100%),
8 dividing the body into four sections: head (10% of person's skin), trunk (30%), upper
9 extremities (20%) and lower extremities (40%). Each area is scored by itself.
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19 10. Physician Global Assessment (PGA): A 5-point ordinal scale used to assess the severity
20 of disease over the body including global, scalp, palmoplantar and nails. The scale
21 ranges from 0 to 4 for global, scalp and palmoplantar assessment [52]:
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26 0= clear: no signs of psoriasis

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28 1= almost clear: only minimal plaque elevation, scaling, and/or erythema

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30 2= mild: slight plaque elevation, scaling, and/or erythema

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32 3= moderate: moderate plaque elevation, scaling, and/or erythema

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34 4= severe: very marked plaque elevation, scaling, and/or erythema
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37 For nails assessment, the scale ranges from 0 to 4:
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40 0= none: normal nail appearance

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42 1= mild: pitting and/or oil drops; mild disfigurement

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44 2= moderate: prominent visible pitting and/or oil drops, distal onycholysis
45 with/without hyperkeratosis; moderate disfigurement
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49 3= severe: pronounced nail changes including pitting, oil drops, distal
50 onycholysis with/without hyperkeratosis, onychodystrophy; substantial
51 disfigurement
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55 4= very severe: severe distal onycholysis with/without hyperkeratosis and/or
56 severe onychodystrophy; prominent disfigurement
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3 11. Physician's satisfaction: A composite survey with 16 items, 10 of them are generic
4 items and correspond to the compassion subscale of the Professional Quality of Life
5 questionnaire [53]; and 6 items were specifically created for this study regarding
6 biological treatment. There are 5-point scales that reflect how frequently the physician
7 experienced this thing in the last 30 days.
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14 12. Patient's and physician's satisfaction of being part of the study: open question to assess
15 the satisfaction that the participation on a clinical study may provide to the patients and
16 physicians.
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22 **Sample size calculation**

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24 A total sample size of 338 patients with baseline WHO-5 score ≤ 50 will provide a 95% power
25 to detect a difference of 10 points [43] in the absolute change from baseline in the WHO-5 total
26 score at week 24, assuming 50.5 as the standard deviation of the difference. This sample size
27 of 338 patients produces a two-sided 95% confidence interval with a precision of ± 5.4 points.
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30 A conservative estimation assumes that 75% of the psoriatic population may have a baseline
31 WHO-5 score ≤ 50 [54]. Therefore, around 450 patients will have to be included in the study to
32 ensure the 338 patients previously described. Also considering a 10% drop out rate, the final
33 number of patients to be included will be approximately 500.
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44 **Data analyses and reporting**

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46 All data analyses will be performed using SAS[®] version 9.2 or higher (SAS Institute, Cary, NC,
47 USA). Descriptive analyses will be performed. Statistical analyses will be based on observed
48 cases. Multiple imputation will be performed as a sensitivity analysis. All AE verbatim terms
49 will be coded using the Medical Dictionary for Regulatory Activities. Medication will be coded
50 using WHO Drug Dictionary. Final analyses will be performed once the data from all patients
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3 have been collected in the database, cleaned, and database lock has occurred. Analyses will be
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5 performed overall and per country.
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8 Changes in WHO-5 (to assess the primary objective) and changes in DLQI-R, PBI-S-10,
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10 TSQM-9, patient's and physician's, and NRS scores will be calculated as the difference
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12 between baseline and follow-up visits (up to 24 months) and will be compared using paired t-
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14 test (or Wilcoxon signed-rank test). Furthermore, all answers will be described by number of
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16 patients who answer in each category or domain (if applicable). To assess the "correlation of
17
18 the change of health-related well-being (WHO-5)", a Pearson product-moment correlation
19
20 coefficient (r) will be used and, for ordinal data, a Spearman's rank-order correlation will be
21
22 used. Work and activity impairment will be analysed using the responses to the WPAI:PSO
23
24 questionnaire in patients actively working in the last 7 days. Activity impairment will be
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26 calculated in each study visit. Changes in WPAI:PSO scores will be calculated as the difference
27
28 between baseline and follow-up visits (up to 24 months) and will be compared using paired t-
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30 test (or Wilcoxon signed-rank test). FamilyPso questionnaire will be described through each
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32 factor and for total score. For additional outcomes, PASI values will be correlated with the
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34 different clinical questionnaires through Pearson correlation (r) in order to assess positive
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36 impact of the control of skin manifestations.
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44 **Patient and public involvement statement**

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46 Patients or the public were not involved in the design of the study, and will not be involved in
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48 the conduct, reporting, or dissemination plans of this research.
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ETHICS AND DISSEMINATION

This non-interventional study will be conducted in compliance with the protocol, all applicable regulatory requirements of the countries where the study is being conducted and the ethical principles of the latest version of the Declaration of Helsinki that are consistent with Good Pharmacoepidemiology Practices. Data protection and privacy regulations will be strictly observed in capturing, forwarding, processing, and storing patient data according to the Directive 95/46/EC on the protection of individuals and in compliance with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). The protocol has been approved by the following ethics committees: (i) Medizinische Universität Graz - Ethikkommission (Austria, reference number: 33-555 ex 20/21), (ii) Comité d’Ethique hospitalo-facultaire (CEHF) Cliniques universitaires Saint-Luc (Belgium, reference number BC-10914), (iii) Comité de Protection des Personnes Nord-Ouest III (France, reference number: 2021-61), (iv) Medizinische Fakultät der Christian-Albrechts-Universität zu Kiel - Ethik Kommission (Germany, reference number: D 480/21), (v) Comitato Etico Università Federico II (Italy, reference number: 295/21), (vi) CEIC Aragón (CEICA) (Spain, reference number: EPA21/016, Acta 11/2021), (vii) Ethikkommission Nordwest- und Zentralschweiz (EKNZ) (Switzerland, reference number: 2021-01705), (viii) DCRF/NWMO Advisory Commission UMC Groningen (The Netherlands, reference number: NWMO 21.09.035), and (ix) London - Hampstead Research Ethics Committee (UK, reference number: 21/PR/0883).

The results of the POSITIVE study will be disseminated through one or more scientific manuscripts and may also be presented at medical congresses.

DISCUSSION

The lack of patient-oriented outcome measures for assessing the overall well-being of patients with psoriasis is becoming a concern in dermatology clinical practice and research. Psoriasis heavily affects the physical, psychological and social well-being of patients and that of their family members and partners, thus, beside clinical assessments, the full impact of psoriasis treatment on the patient and people around should be recognised. To our knowledge, the POSITIVE study is the first study to apply the WHO-5 as a primary endpoint to estimate the improvements on patients' well-being treated with tildrakizumab in a real-world setting. This study will measure the well-being of patients, their partners and of physicians, for a better understanding of the impact of psoriasis as a chronic disease on patients and their close environment. The results of this study could potentially be added to the available psoriasis evaluation methods and provide dermatologists with new tools to improve their own and patient's well-being enhancing patient-clinician relationships. The need to provide results from the POSITIVE study becomes essential given the WHO claim for people-centred healthcare and patient commitment. The POSITIVE study will significantly promote patients' involvement and awareness as recommended by the WHO global report on psoriasis [5], as the most common root for patient dissatisfaction is being poorly engaged in the treatment decision-making process. Limitations of the study will include potential bias and missing information or possible drop-outs or lost to follow-up in the last follow-up visits of the study because of the long observational period. In addition, potential time-related maturation/history effects on the primary outcome measure of general well-being should be considered, especially post-pandemic, given the long observational period and the lack of a control group. Moreover, patients included in this study will have to be preselected to initiate tildrakizumab therapy before patient inclusion in the study. Finally, a limitation could be represented by patient-related bias on self-perception of well-being due to the inclusion in a clinical study.

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3 In summary, this prospective observation study constitutes an innovative people-centric
4 approach to investigate how intervention with tildrakizumab may improve the well-being of
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6 patients, their families, and healthcare professionals.
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For peer review only

ETHICS STATEMENT

Patient consent for publication

Not required.

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CONTRIBUTORSHIP STATEMENT

MA, RS, ED, PL, EdJ, GF, LN, AN, JL, ZR, SG, EM, TO, IK, and UM were involved in conception and study design. **MA, RS, ED, PL, EdJ, GF, LN, AN, JL, ZR, SG, EM, TO, IK, and UM** provided edits, critiqued the manuscript for intellectual content, and approved the final manuscript.

COMPETING INTERESTS

MA has served as consultant for, or has been a paid speaker for clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including Abbvie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Eli-Lilly, GSK, Janssen-Cilag, Leo Pharma, Medac, Merck, MSD, Novartis, Pfizer, UCB, and Xenoport; **RS** has been an advisor and/or received speaker honoraria and/or received grants from AbbVie, Almirall, Beiersdorf, Janssen, LEO Pharma and Novartis; **ED** has the following conflict of interests: Advisory Board member, consultant, grants, research support, participation in clinical trials, honorarium for speaking, research support, with the following pharmaceutical companies: Abbvie/Abbott, Almirall, Amgen, Janssen-Cilag, Leo Pharma, Novartis, Pfizer, MSD-Schering-Plough, Celgene, Lilly, and UCB; **PL** received honoraria and/or grants as an investigator, speaker, and/or advisory board member for AbbVie, Almirall, Actelion, Celgene, Janssen, Lilly, Sanofi, Leo, UCB, and Novartis; **EdJ** has received research grants for the independent research fund of the department of dermatology of the Radboud University

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3 Medical Center Nijmegen, The Netherlands from AbbVie, Leo Pharma, Janssen
4
5 Pharmaceuticals, Novartis, Pfizer, and UCB and has acted as consultant and/or paid speaker for
6
7 and/or participated in research sponsored by companies that manufacture drugs used for the
8
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15 Medical Center Nijmegen (Radboudumc), The Netherlands; **GF** has acted as speaker and
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17 consultant for AbbVie, Almirall, Eli Lilly, Leo Pharma, Janssen, Novartis, and UCB; **LN**
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22
23 and/or receiving speaking fees and/or grants and/or served as an investigator in clinical trials
24
25 for AbbVie, Almirall, Amgen, BMS, Boehringer Ingelheim, Celgene, Eli Lilly, Galderma,
26
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34
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36
37 received speakers' honoraria and/or received grants and/or participated in clinical trials of the
38
39 following companies: AbbVie, Affibody AB, Akari Therapeutics Plc, Almirall-Hermal,
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41 Amgen, Anaptys Bio, Argenx BV, AstraZeneca AB, Biogen Idec, Bioskin, Boehringer-
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43 Ingelheim, Celgene, Dermira, Eli Lilly, Forward Pharma, Galderma, Hexal AG, Incyte Inc.,
44
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46
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48
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50
51 employees of Almirall; **TO** has served as medical advisor for Almirall; **UM** has been an advisor
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3 and/or received speakers' honoraria and/or received grants and/or participated in clinical trials
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5 of the following companies: AbbVie, Aditxt, Almirall, Amgen, Aristeia, Boehringer-Ingelheim,
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7 Bristol-Myers Squibb, Celgene, Dr. Reddy's, Eli Lilly, Foamix, Formycon, Immunic, Janssen,
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19 **DATA SHARING STATEMENT**

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21 Not applicable.
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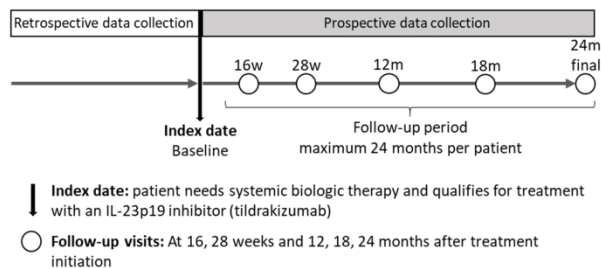
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3 **FIGURE LEGENDS**
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5 **Figure 1.** Study design of the POSITIVE study
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