Psoriasis: Targets and Therapy

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ORIGINAL RESEARCH

Patient-Reported Well-Being in Value-Based Routine Care in Psoriatic Disease Using Tildrakizumab: 2-Year Data of the Phase IV POSITIVE Study

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Purpose: Psoriasis extends beyond skin manifestations and significantly impacts patients' psychological health, social interactions, and daily functioning. The main objective was to assess the 2-year effect of tildrakizumab, an interleukin-23p19 inhibitor, on the skin, the psychological well-being and the health-related quality of life (HRQoL) of people with psoriatic disease in real-world.

Patients and Methods: The POSITIVE study is a 24-month, prospective observational multinational study enrolling adults with moderate-to-severe plaque psoriasis treated with tildrakizumab according to clinical practice. Outcome measurements included the 5-item WHO Well-being Index (WHO-5), Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index-Relevant (DLQI-R).

Results: 785 patients were included. The mean (95% CI) WHO-5 score increased from 53.7 (52.2, 55.3) at baseline to 63.2 (61.5, 64.8) at W16 and continued improving over time: 65.9 (64.0, 67.9) at W52 and 70.4 (68.1, 72.7) at W104. The mean (95% CI) PASI decreased from 12.9 (12.3, 13.5) at baseline to 2.4 (2.2, 2.7) at W16 and was maintained until W104 [1.3 (1.1, 1.5)]. At W104, 87.9/79.0/65.1% of patients maintained PASI ≤3/≤2/≤1. Drug survival due to lack of effectiveness or adverse events (AE) was 87.8% and 96.3% after 2 years. The mean (95% CI) DLQI-R score decreased from 12.0 (11.4, 12.6) at baseline to 3.1 (2.6, 3.6) W52 and 2.1 (1.7, 2.5) at W104. At the final analysis, 11.1% of patients had ≥1 related AE.

Conclusion: Treatment with tildrakizumab delivered sustained and holistic long-term health for moderate to severe psoriasis over 2 years by consistently improving patients' psychological well-being, life and clinical outcomes with a favourable safety profile.

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Keywords: psoriasis, real-world evidence, tildrakizumab, well-being, effectiveness, long-term control, safety, WHO-5

Introduction

Psoriatic disease is a chronic immune-mediated inflammatory condition affecting more than 60 million people worldwide with a prevalence of 2–3%.[1–3] Beyond the visible manifestations, psoriasis significantly impacts patients' overall lives, including their psychological state,[4] intimate and other social relationships,[5] occupational functioning,[6] as well as

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impacting on family members.[7,8] The psychosocial burden of psoriatic disease is particularly profound, with patients experiencing higher rates of depression,[9] and even suicidal ideation compared to the general population.[10,11]

The World Health Organization (WHO) defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".[12] Despite skin clearance remaining the primary objective, this definition underscores the importance of considering well-being - not just absence of disease - as an ultimate goal in healthcare. Thus, this perspective encourages a shift from focusing solely on skin clearance and HRQoL to embracing a more comprehensive view of patient health that also includes the assessment of the psychological well-being to ensure overall health.[13–15] The WHO-5 is a generic (not disease specific) validated and widely used questionnaire across different chronic diseases, such as diabetes mellitus, cancer or mental disorders, and offers a more holistic approach to measuring psychological health-related well-being.[16,17]

Tildrakizumab, a humanized monoclonal antibody targeting the p19 subunit of interleukin(IL)-23, has demonstrated efficacy and a favourable safety profile in treating psoriatic disease in large scale randomized controlled Phase III trials (reSURFACE 1 and reSURFACE 2) for up to 5 years.[18,19] Tildrakizumab has also demonstrated exceptional drug-survival in the treatment of moderate-to-severe psoriasis in routine clinical practice.[20–23]

The POSITIVE ("Patient-reported wellbeing using tildrakizumab in a live setting") study represents a novel approach in psoriasis research by holistically assessing impact on the patient and his/her environment: through a vast range of outcomes: long-term patient-reported well-being (WHO-5 as a primary endpoint), effectiveness (PASI, PGA), and HRQoL (DLQI-relevant); patient's treatment satisfaction (TSQM-9), and treatment-related patient benefits (PBI-S-10); work impairment due to psoriatic disease (WPAI:PSO), and extent of the skin manifestations on the entire body using a "heat map", as well as the impact on partners (FamilyPsO) and treating physicians (physicians' well-being).[23] Whilst the 52-week interim results have been reported previously,[24] the present manuscript presents the 2-year findings from the POSITIVE study, offering valuable insights into the long-term effects of tildrakizumab on various aspects of patients' health in a real-world setting.

Materials and Methods

Study Design

POSITIVE is a 24-month, multinational, prospective observational phase IV study in adult patients with moderate-to-severe plaque psoriasis who require systemic biologic therapy and qualify for treatment with tildrakizumab in real-world clinical practice.

Patients aged 18 years or older with diagnosis of moderate-to-severe chronic plaque psoriasis documented in the medical chart who needed systemic biologic therapy and qualified for treatment with an IL-23p19 inhibitor were included. Patients unable to comply with the requirements of the study or who, in the opinion of the study physician (ie patients unable to provide written informed consent) or patients included in other clinical trials were excluded.

Participating countries as well as details of the study design and ethics committees that approved the study, have been previously reported.[23]

The study assessments for this final analysis (up to 24 months) encompassed outcomes reported by patients, their partners, and the physicians at baseline, weeks 16, 28, and 52, and months 18 and 24.

Outcomes of the Study

Full details of the assessments can be found elsewhere.[23] Here, we are reporting the long-term assessment of the main endpoints of the study: PASI, WHO-5, DLQI-R, NRS of psoriasis-related symptoms, PGA for high impact areas, treatment goals (PBI) and satisfaction (TSQM-9) and safety outcomes.

The WHO-5, primary endpoint of the study, is a global rating scale measuring subjective well-being by positive assertions. The respondent is asked to rate the extent to which each of the five items applies to him/her in the last 2 weeks from 5 (all the time) to 0 (none of the time). The standardized score ranges from 0 to 100, where 100= "maximal well-being".[16,25]

DLQI 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.[26] 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.[27]

Efficacy in treating psoriatic disease lesions was evaluated by the physician assessing the PASI score (0–72).[28]

Safety

Adverse events (AEs), and treatment-related AEs, with their degree of severity, were collected. All AE terms were coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities. The number of withdrawals and discontinuations were also reported.

Statistical Analysis

The Full Analysis Set (FAS) has been used for all the efficacy endpoints, and the Safety Analysis Set (SAS) for all safety outcomes.

Due to the observational and descriptive nature of this study, the main analyses were done using the observed cases (OC). In order to handle bias related with missing values and as sensitivity analyses, last observation carried forward (LOCF) and multiple imputation (MI) approaches were also applied for efficacy outcomes.

Usual descriptive statistics were performed to report the data, including the change from baseline, if applicable, in the different questionnaires at every visit. Drug survival was determined through Kaplan-Meier method. Two-sided Wilcoxon Signed-Rank tests were used to evaluate the change from baseline. Given that no confirmatory testing was planned in this study, the provided p-values are descriptive representations of the data.

All data analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina, USA). Venn diagrams were done using RStudio with R version 4.2.1.

Results

Baseline Characteristics

A total of 785 moderate-to-severe patients with plaque psoriasis were analysed (FAS population). Demographic and baseline characteristics are shown in Table 1 and are in line with previous real-life studies.[20] A total of 277 (35.3%) patients were women, and the mean (95% Confidence Interval, 95% CI) age was 46.9 (45.9, 48.0 years). The mean (95% CI) disease duration was 14.9 years (14.0, 15.8). Most of the patients (95.2%) initiated the tildrakizumab treatment with the 100 mg dose.

The distribution of patients per country was the following: 193 (24.6%) from France, 183 (23.3%) from Germany, 108 (13.8%) from Spain, 88 (11.2%) from Austria, 69 (8.8%) from Switzerland, 57 (7.3%) from Italy, 38 (4.8%) from Belgium, 28 (3.6% from United Kingdom, and 21 (2.7%) from Netherlands.

Psychological Well-Being

The mean (95% CI) WHO-5 score at baseline was 53.7 (52.2, 55.3). As early as 16 weeks of treatment, the WHO-5 score increased to 63.2 (61.5, 64.8), restoring well-being levels back to the general population (mean of 64.9) [Figure 1].[29] There was a further gradual improvement throughout the study, with scores of 64.9 (63.2, 66.6), 65.9 (64.0, 67.9), 67.6 (65.4, 69.7) and 70.4 (68.1, 72.7) at weeks 28, 52, 78 and 104 [($p<0.001$ for all)]. The mean score at the end of the study surpassed the mean of the European general population, suggesting that long-term control of the disease, has a deep positive impact on the mental health of the patients.[29] The overall risk of depression (WHO-5<50) significantly decreased from 41.5% at baseline to 23.8% at week 16, 19.4% at week 52 and 17.0% at week 104 ($P<0.05$ for all).

Clinical Response

The mean (95% CI) Psoriasis Area and Severity Index (PASI) significantly decreased from 12.9 (12.3, 13.5) at baseline to 2.4 (2.2, 2.7) at week 16 and 1.7 (1.5, 1.9) at week 28 and maintained throughout the study: 1.5 (1.3, 1.8) at week 52 and 1.3 (1.1, 1.5) at week 104 ($p<0.001$ for all) (Figure 2).

Table 1 Demographic and Other Baseline Characteristics of the 785 Patients

Variable	
Gender, N (%) (female)	277 (35.3%)
Age (years), mean (95% CI)	46.9 (45.9, 48.0)
Weight (kg), mean (95% CI)	84.0 (82.7, 85.4)
BMI (kg/m^2), mean (95% CI)	27.9 (27.6, 28.3)
Smoking habit, N (%)	
Non-smoker	298 (38.0%)
Ex-smoker	159 (20.3%)
Current smoker	289 (36.9%)
Unknown	38 (4.8%)
Years since 1st diagnosis of the disease, mean (95% CI)	14.9 (14.0, 15.8)
Location of plaque psoriasis at diagnosis	
Nails	277 (35.4%)
Palms	156 (19.9%)
Soles	106 (13.5%)
Scalp	512 (65.4%)
Genitalia	219 (28.0%)
Flexures	244 (31.2%)
Other	349 (44.6%)
Co-morbidities at inclusion date	383 (48.9%)
High blood pressure	163 (20.8%)
Psoriatic arthritis	83 (10.6%)
Depression	69 (8.8%)
Dyslipidaemia	65 (8.3%)
Diabetes Mellitus	63 (8.0%)
Fatty liver disease	43 (5.5%)
Cardiovascular disease	42 (5.4%)
Metabolic syndrome	25 (3.2%)
Kidney disease	14 (1.8%)
Neoplasm	10 (1.3%)
Inflammatory bowel disease	3 (0.4%)
Psoriasis Drug therapy history	
Topicals	455 (58.0%)
Phototherapy	274 (34.9%)
Systemic non-biologic	430 (54.8%)
Biologic	249 (31.7%)

Abbreviations: N, number of patients; BMI, body mass index; 95% CI, 95% Confidence interval.

The proportion of patients achieving PASI ≤3/≤2/≤1 responses was 73.3%/60.9%/41.3% at week 16, 85.3%/73.9%/54.4% at week 28, 86.6%/77.5%/59.7% at week 52 and 87.9%/79.0%/65.1% at week 104 (Figure 2).

The drug survival of tildrakizumab with adverse events or ineffectiveness as an event was 97.8% and 92.9% at year 1, and 96.3% and 87.8% after 2 years, respectively (Figure 3). These proportions represent the percentage of patients who remained on therapy among those with available follow-up data for each outcome.

Health-Related Quality of Life (HRQoL)

HRQoL was evaluated using the well-established DLQI questionnaire, however, here we used a recently developed scoring that adjusts the total score of the questionnaire for the number of "not relevant" responses as indicated by a patient (DLQI-R).[27]

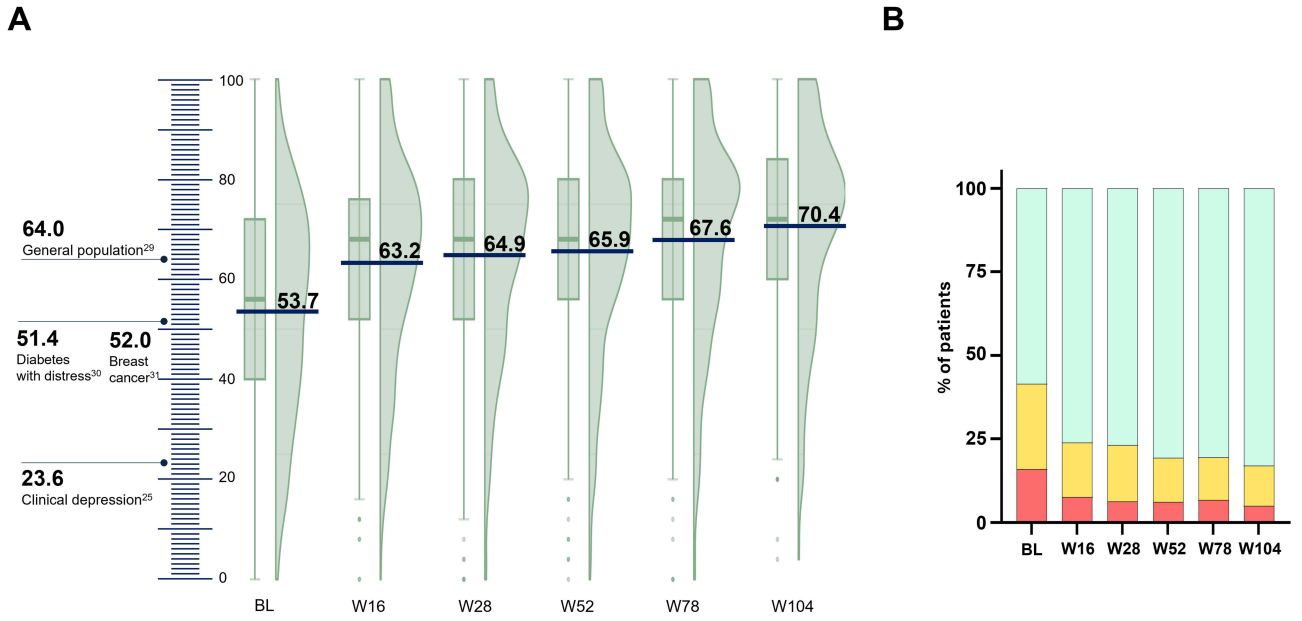

Figure 1 Representation of the World Health Organization-Five Well-Being Index (WHO-5) scores up to Week 104. (**A**) Left side, mean score in the general population and other representative diseases. Right side, in green, distribution of scores (observed cases) is visualised using box-and-whisker plots overlaid with violin plots, showing quartiles, median, range, and probability density. Dark blue horizontal lines and numbers represent the mean scores. MI and LOCF sensitive analysis are shown in Table S1. (**B**) % of patients in each WHO-5 category: 0–28 (red), 29–50 (yellow), 51–100 (green).
Abbreviations: BL, baseline; W, week.

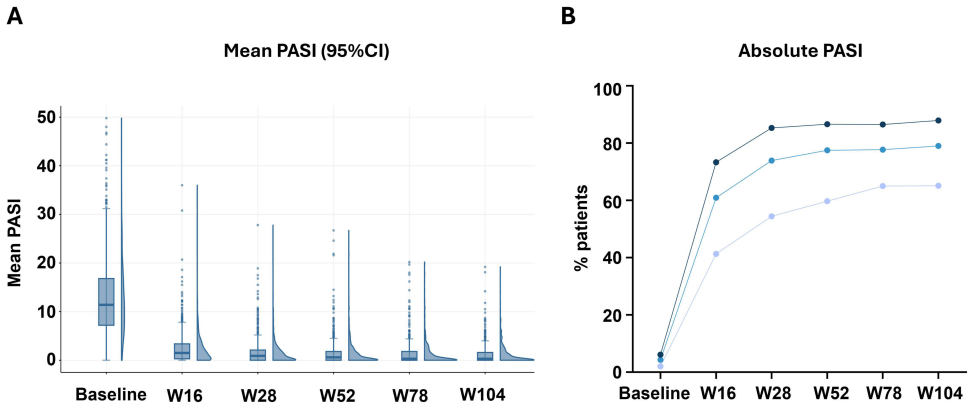

Figure 2 PASI evolution. (**A**) Mean absolute PASI scores up to Week 104 (observed cases). Distribution of scores is visualised using box-and-whisker plots overlaid with violin plots, showing quartiles, median, range, and probability density. Dark blue horizontal lines represent the mean scores. (**B**) Percentage of patients achieving PASI≤ 3 (dark blue) PASI ≤2 (blue) and PASI ≤1 (light blue). MI and LOCF sensitive analysis are shown in Table S1.
Abbreviations: PASI, Psoriasis Area and Severity Index.

The mean (95% CI) DLQI-R significantly decreased over the 2-year period, from 12.0 (11.4, 12.6) to 4.3 (3.8, 4.7), 3.3 (2.9, 3.7), 3.1 (2.6, 3.6) and 2.1 (1.7, 2.5) at weeks 16, 28, 52 and 104, respectively ($p<0.001$ for all) (Figure 4).

When using the DLQI-R approach, the thresholds for no effect or small effect scores are rounded to two decimal places.[27] The proportion of patients achieving DLQI-R 0–1.99 (no effect) was 37.7% at week 16, 46.6% at week 28, 54.2% at week 52 and 62.3% at week 104 (Figure 4).

Holistic Management of the Psoriatic Disease

Following the WHO definition of health,[12] we assessed the number of patients with skin (PASI), HRQoL (DLQI-R) and psychological well-being (WHO-5) improvements throughout the study (see Table S1 for absolute mean PASI, DLQI-R and WHO-5). The thresholds used to define disease control were: PASI ≤2,[30] DLQI-R 0–1.99,[27] and WHO-5 ≥64.[29] As

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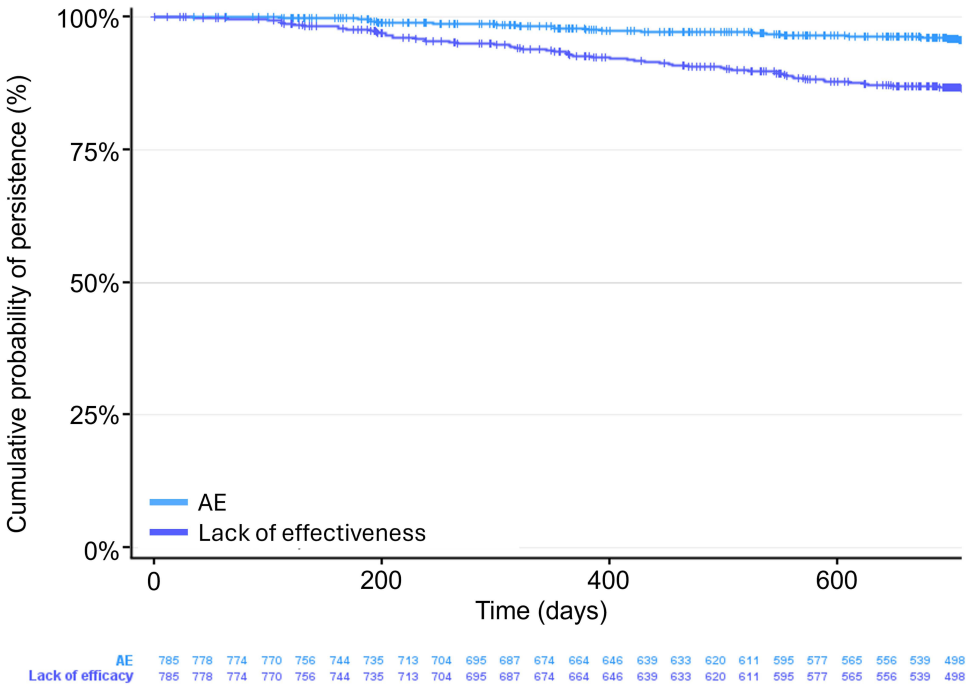

Figure 3 Drug survival of tildrakizumab over 24 months (730 days), Kaplan Meyer Curves related to discontinuation due to adverse events (light blue) and lack of effectiveness (dark blue).

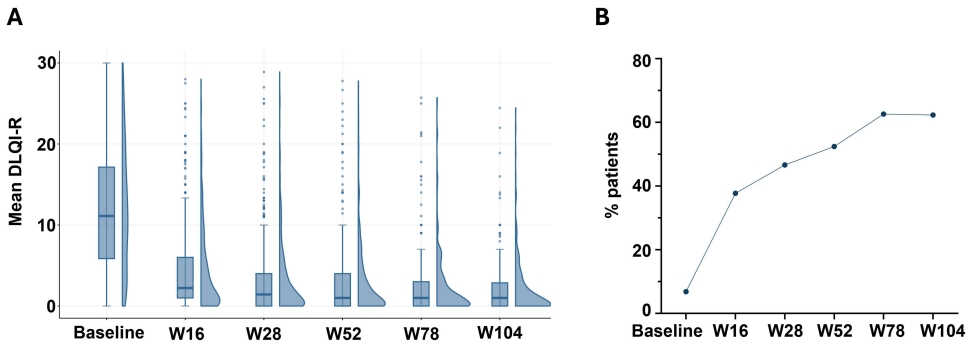

Figure 4 DLQI-R. (**A**) Mean absolute DLQI-R scores up to Week 104 (observed cases). Distribution of scores is visualised using box-and-whisker plots overlaid with violin plots, showing quartiles, median, range, and probability density. Dark blue horizontal lines represent the mean scores. (**B**) Percentage of patients achieving DLQI-R 0–1. *Mean change from baseline ($p<0.0001$). MI and LOCF sensitive analysis are shown in Table S1.
Abbreviations: DLQI-R, Dermatology Life Quality Index - Relevant.

expected, the disease-related goals (PASI and DLQI-R) at baseline were achieved by a minority of patients (4.6% and 6.8%, respectively); whilst 39.5% of the patients conserved a psychological well-being similar than the population norms (Figure 5A). In general, patients reported high levels of improvement in all three domains at week 16 (Figure 5B), which increased throughout the study (Figure 5C and D). Whilst skin rapidly improved and remained controlled in most of the patients over the two-year period, HRQoL and psychological well-being showed slower improvements (Figure 5A–D). In total, 24.9%, 33.9%, 37.1% and 44.8% of the patients reached the three combined goals in after 16, 28, 52 and 104 weeks.

Safety

During the 24-month study period, 86 (11.1%) of patients in the SAS population (n= 778) had ≥1 related AE, with 7.2% classified as mild and 3.6% as moderate. The most common related AEs were infections and infestations (31%), gastrointestinal disorders (1.2%) and injection site reactions (0.6%).

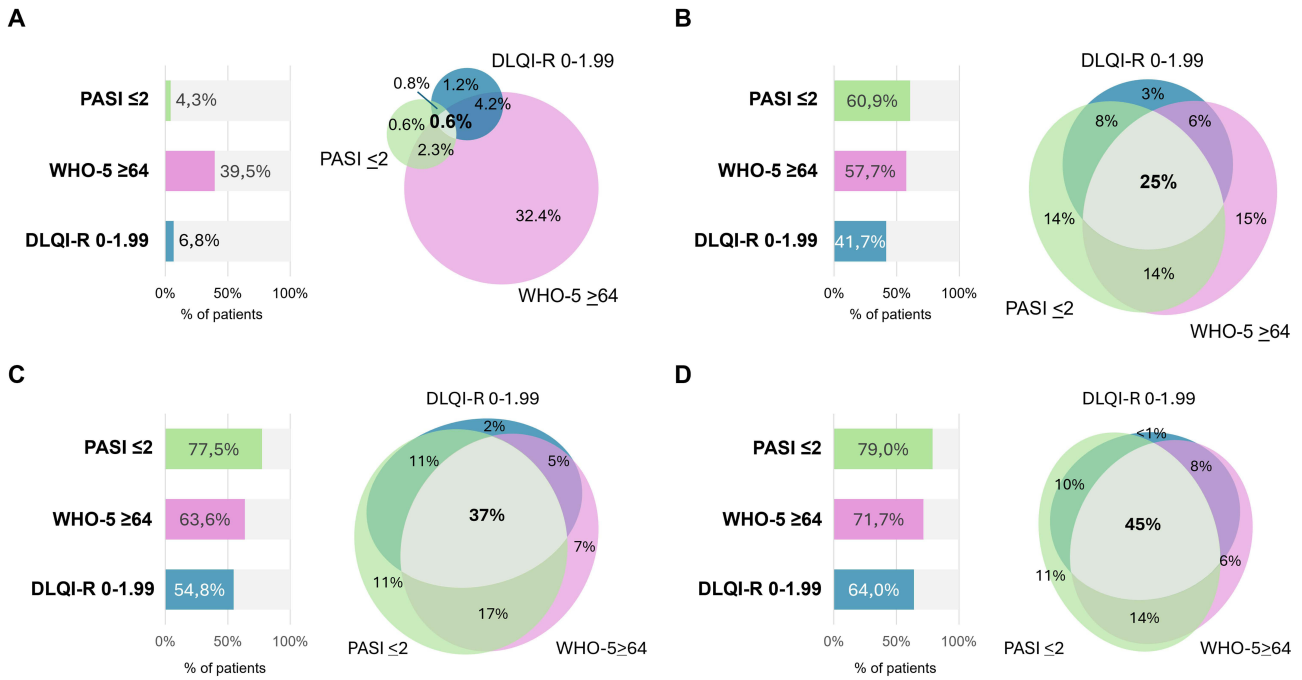

Figure 5 Patient-centred care. (**A**–**D**) represent data at baseline, weeks 16, 52 and 104, respectively. For each panel, the left plot indicates the percentage of patients achieving each of the threshold's for skin, quality of life and psychological well-being (PASI ≤2,[30] DLQI-R 0–1.99,[27] and WHO-5 ≥64),[29] respectively. Right plots for each panel represent a Venn diagram with the patients achieving all the three goals (centre) and other combinations.

The percentage of patients who dropped out of the study for any reason up to month 24 was 32.3%; 12.2% were due to lack or loss of effectiveness, and 3.6% due to an AE, and the rest due to lost to follow-up (7.6%), poor compliance to protocol (1.8%), patient's decision (4.6%) or other reasons (2.5%).

Discussion

In an era where most advanced treatments achieve high levels of skin clearance for psoriatic disease,[20] the POSITIVE study represents a paradigm shift by choosing patient-reported psychological well-being as its primary endpoint whilst demonstrating excellent long-term skin control over a 2-year period. This approach aligns with contemporary models of value-based healthcare and the WHO's holistic definition of health, which extends beyond the mere absence of disease.[12] By collecting comprehensive long-term data on physical, social and psychological well-being, this study provides unique insights into the long-term benefits of tildrakizumab in real-world clinical practice.

In our previous interim data, we have shown that moderate-to-severe psoriatic disease significantly impacts psychological well-being,[24] with baseline WHO-5 scores (mean 54.0) substantially lower than those of the general European population (mean 64.9) and comparable to patients with type 2 diabetes with distress (51.4)[31] or breast cancer (52.2).[32] Here, we confirmed these results in a larger sample size (785 patients) and a longer maintenance period, confirming that tildrakizumab provides durable benefits for the patients´ psychological well-being. The observation that the mean score at the end of the study exceeded the mean of the general population, might suggest that sustained long-term disease control, allowed patients and, in part, partners to regain a normal life in the absence of visible disease.[30]

The first treatment goal for patients when treating uncontrolled psoriatic disease, is to improve their skin.[33] Here we show that the short-term improvement (with 7 out of 10 patients [73.0%] reaching the recently suggested clinically meaningful target of PASI ≤2 at week 28)[34] was maintained throughout the 24 months of tildrakizumab treatment (79.0%), reinforcing the long-term effectiveness previously published.[20–22] The effectiveness and safety profile of tildrakizumab is reflected in the drug survival data. At the end of the 2-years, only 12.2% of the patients required treatment change due to lack or loss of effectiveness, and 3.7% due to adverse events. These results further support the findings from another real-world study reporting similar survival rates over a 4-year period.[22]

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The main outcomes in most of clinical studies are fixed endpoints such as the proportion of patients achieving PASI ≤3 or ≤2. However, these endpoints do not capture the full range of clinical benefits in daily practice and might consider patients with a poor psychological well-being as well-controlled patients, whilst they may have impaired health despite the absence of skin manifestations. In our view, and supported by the data from the POSITIVE study, a combination of clinical and patient-reported outcomes would be optimal to decide upon treatment success, with WHO-5 being a complementary addition to skin outcomes and DLQI. We defined clinically relevant responses based on thresholds of the three major domains: skin signs (PASI), HRQoL (DLQI-R) and psychological well-being (WHO-5). 83.9% of the tildrakizumab-treated patients reported clinically relevant improvement in at least one of the three domains with 24.9% of them improving all three domains in only 16 weeks, 37.1% after one year, and nearly half of the patients (44.8%) after two years. Interestingly, the fact that most of the patients improved their skin rapidly but not all improved the social nor psychological well-being, suggests that there might be a delay between physical and psychological improvement in patients with skin disease.[35] This phenomenon, named "psycholag", needs to be further explored and highlights the complex interplay between the absence of disease and the health restoration.[35]

To our knowledge, the POSITIVE study represents the first comprehensive demonstration of a biologic therapy addressing several domains (physical, emotional, social and functioning) that could impact the Cumulative Life Course Impairment (CLCI) in psoriasis.[36,37] While detailed analyses of individual endpoints will be reported in dedicated publications, here we report a consistent and sustained achievement of clinically meaningful improvements across skin manifestations, high-impact anatomical areas, debilitating symptoms (itch, pain, joint pain and fatigue), psychological well-being, quality of life, treatment satisfaction, and partner burden. This entire spectrum over 2 years, demonstrates that tildrakizumab delivers truly holistic disease control that extends beyond traditional skin-centric outcomes to address the complete burden of psoriatic disease on patients' lives.

This study has several limitations. The open-label design may have introduced bias in reported outcomes. Additionally, the absence of a control group makes it difficult to distinguish treatment effects from natural disease fluctuations or placebo effects. However, the magnitude and consistency of improvements across multiple domains and timepoints suggest a genuine treatment effect. Another limitation is that the missing data could introduce bias on the results. To ensure that the missing data is completely at random (MCAR), we implemented two different imputation methods (LOCF and MI) that can effectively mitigate this risk by preserving the underlying distributional characteristics of the dataset whilst accounting for uncertainty in the missing values, as demonstrated by sensitivity analyses comparing results across both techniques. For all the three questionnaires (WHO-5, PASI and DLQI-R), the results were very similar across the different analysis (OC, LOCF and MI), confirming the absence of induced bias. Moreover, whilst we collected comprehensive data on various aspects of well-being, we did not explore potential mediators or moderators of treatment response, which would be valuable for personalized medicine approaches.

Despite these limitations, the POSITIVE study makes several important contributions to the field. By demonstrating sustained improvements in skin, HRQoL and psychological well-being over 2 years, this study establishes the long-term value of tildrakizumab beyond skin clearance only. These findings underscore the importance of incorporating psychological well-being on top of the clinical and HRQoL outcomes, in order to assess the patient's health, moving beyond traditional efficacy measures to embrace a more holistic view of treatment success.

Conclusion

The POSITIVE study demonstrates that tildrakizumab provides sustained benefits across multiple domains of health over two years in patients with moderate-to-severe plaque psoriasis. The durable improvements in skin clearance, psychological well-being and HRQoL, combined with a favourable safety profile, support the long-term value of tildrakizumab in real-world clinical practice.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Statement of Ethics

This study was approved by ethics committees at each participating country and is being conducted in accordance with the ethical principles of the latest version of the Declaration of Helsinki that are consistent with Good Pharmacoepidemiology Practices and local applicable laws and regulations. Written informed consent must be given by patients prior to data collection. The protocol has been approved by the following ethics committees: (1) Medizinische Universität Graz - Ethikkommission (Austria, reference number: 33-555 ex 20/21), (2) Comité d'Ethique hospitalo-facultaire (CEHF) Cliniques universitaires Saint-Luc (Belgium, reference number BC-10914), (3) Comité de Protection des Personnes Nord-Ouest III (France, reference number: 2021-61), (4) Medizinishe Fakultät der Christian-Albrechts-Universität zu Kiel - Ethik Kommission (Germany, reference number: D 480/21), (5) Comitato Etico Università Federico II (Italy, reference number: 295/21), (6) CEIC Aragón (CEICA) (Spain, reference number: EPA21/016, Acta 11/2021), (7) Ethikkommission Nordwest- und Zentralschweiz (EKNZ) (Switzerland, reference number: 2021-01705), (8) DCRF/NWMO Advisory Commission UMC Groningen (The Netherlands, reference number: NWMO 21.09.035) and (9) London - Hampstead Research Ethics Committee (UK, reference number: 21/PR/0883).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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