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# A long-term, prospective, observational cohort study of the safety and effectiveness of etanercept for the treatment of patients with paediatric psoriasis in a naturalistic setting

*Background:* Psoriasis is a chronic inflammatory skin disorder that affects 125 million people worldwide, with one-third having childhood onset. *Objectives*: The PURPOSE study evaluated long-term safety and effectiveness of etanercept in paediatric psoriasis. *Materials & Methods*: This observational study enrolled patients with paediatric psoriasis who were prescribed etanercept per routine care in eight EU countries. Patients were followed retrospectively (first dose prior to 30 days before enrolment) or prospectively (first dose within 30 days prior to or any time after enrolment) for five years. Safety endpoints included serious infections, opportunistic infections, malignancies, other serious adverse events (SAEs) and adverse events. Effectiveness endpoints (prospective patients) included treatment patterns, dose change/discontinuation, and physicians' global subjective assessment of change in disease severity from baseline to follow-up. *Results*: In total, 72 patients were enrolled (32 prospectively, 40 retrospectively), with mean age of 14.5 years and mean disease duration of 7.1 years. No serious or opportunistic infections/malignancies were reported. Psoriasis ($n$=8) and subcutaneous tissue disorders (system organ class) (erythema nodosum, erythrodermic psoriasis; $n$=1 for each) were the most frequently reported SAEs, which occurred in six (8.3%) patients with current/recent treatment and four (7.4%) with previous treatment. Of 25 treatment-emergent SAEs, seven (28.0%) were possibly related to etanercept. Assessments of prospective patients revealed that 28 (87.5%) completed 24 weeks, five (15.6%) required at least one subsequent course, and 93.8% experienced decreased disease severity. It is possible that some rare adverse events were not noted in this relatively small sample. *Conclusion*: These real-world data are consistent with the known safety and efficacy profile of etanercept in paediatric patients with moderate to severe plaque psoriasis.

**Key words:** paediatric dermatology, psoriasis, etanercept, safety, effectiveness

Psoriasis is a chronic inflammatory immune-mediated skin disorder [1], often leading to a physical, emotional, and social burden, resulting in impaired quality of life [2]. Globally, psoriasis affects 125 million people, or 2-3% of the population [3]. Nearly one-third of patients develop psoriasis in childhood [4]. The worldwide prevalence of psoriasis in children is estimated at up to 1.4% [5], with a 0.5-1.0% prevalence in Europe [6].

While the majority of patients with mild to moderate psoriasis manage the disease with topical medications or phototherapy, this may be insufficient for patients with moderate to severe disease [7]. Biologic agents are associated with a high benefit-to-risk ratio and are a favourable treatment option in the management of moderate to severe psoriasis in adults [7]. For paediatric psoriasis, most of the literature indicates that biologic treatment shows efficacy for moderate to severe plaque psoriasis [8].

Etanercept is a tumour necrosis factor (TNF) alpha inhibitor, first approved in 1998 by the US Food and Drug Administration for adults with moderate to severe rheumatoid arthritis [9]. Subsequently, it was approved for treatment of moderate to severe juvenile idiopathic arthritis (JIA) (aged 4-17 years) [10]. In patients with JIA, etanercept has shown a favourable long-term safety profile; studies suggest that repeated etanercept treatment for up to eight years was not associated with an

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increase in serious adverse events (SAEs) [11, 12]. Etanercept has also shown a favourable benefit-risk profile in adults with moderate to severe plaque psoriasis [13]. The European Commission extended the marketing authorization for treatment of chronic severe plaque psoriasis in children and adolescents (8-17 years of age) in 2008 [14], and patients from six years of age in 2011 [15].

Due to the mechanism of action and role of TNF in immune and inflammatory response function, there is an increased risk for opportunistic and/or serious infections [16]. Because of clinical and post-marketing experience across indications, current US product labelling and European Union (EU) prescribing information for etanercept includes a special warning addressing the risk of serious infections, sepsis, tuberculosis, and opportunistic infections [17]. A standard course of etanercept treatment is expected to last up to 24 weeks with a recommended dose of 0.8 mg/kg weekly and a maximum dose of 50 mg per week. Since etanercept is not curative, patients may receive repeated courses during disease flares. Nevertheless, there is limited published literature regarding the risk of long-term adverse events (AEs) associated with chronic repetitive administration in patients with paediatric plaque psoriasis in the real-world setting.

PURPOSE (Paediatric Registry of Psoriasis and Enbrel) was designated by the European Medicines Agency as a post-authorization safety study (PASS) to evaluate the long-term safety of etanercept in patients with paediatric plaque psoriasis, as well as the effectiveness of etanercept in routine clinical practice.

## Materials and methods

This study was a multicentre, long-term, observational cohort PASS conducted to evaluate the long-term safety and effectiveness of etanercept prescribed by dermatologists to children for the treatment of plaque psoriasis. To optimize enrolment and representativeness, systematic selection of participating EU countries and dermatology clinics was guided by country-specific psoriasis prevalence rates, market uptake, and availability of etanercept. A total of 174 investigators in 11 countries were invited to participate, resulting in patients enrolled at 28 sites in eight EU countries (Germany, Italy, Netherlands, France, Hungary, Spain, Greece, and Portugal). Prospective data were collected from patient interviews and by treating physicians, while retrospective data were collected by medical record abstraction. Follow-up visits were scheduled every three months during the first two years, and every six months thereafter. Each patient was expected to participate for five years, or until the registry completed in 2018, whichever came first.

This study was conducted to provide information regarding the long-term safety of etanercept use in paediatric patients with plaque psoriasis in routine clinical practice. As such, there was no dispensing of study medication or protocol-specified procedures associated with participation in this study. All medical treatment including medication regimen was solely at the discretion of the treating physician in accordance with their usual care. The recommended course of etanercept treatment for paediatric psoriasis is 24 weeks; physicians were advised to consider discontinuation of etanercept if a satisfactory response was not achieved by 12 weeks. If a patient received etanercept for less than 24 weeks, the physician was asked to report the reason for early discontinuation of therapy whether for positive (*e.g.*, clearing of plaque psoriasis) or negative reasons (*e.g.*, intolerance, adverse event, less than expected therapeutic effect). Treatment discontinuation due to lack of desired therapeutic effect, for purposes of analysis, served as a proxy for treatment effectiveness. As etanercept treatment is not curative for this chronic condition, patients were likely to require repeated courses of etanercept over time. For each subsequent course of etanercept, the occurrence of, and reasons for premature discontinuation, *i.e.*, less than 24 weeks, were documented. If a subsequent course of systemic therapy did not include etanercept, the reason for that decision was documented.

The registry was designed for open enrolment of all paediatric patients taking etanercept at any registry site. The population for safety analysis included all patients who received at least one dose of etanercept. Safety endpoints included serious infections, opportunistic infections, and malignancies. All other SAEs and non-serious AEs occurring during the study period were collected and coded using the Medical Dictionary for Regulatory Activities (MedDRA v14.0). Any potential safety endpoints were adjudicated by the registry's Endpoint Committee.

Effectiveness endpoints were intended to be descriptive and were inferred from patterns of treatment, including changes in treatment, discontinuation of etanercept during and after initial treatment period, use of various immunosuppressants and systemic therapies, and reason for change in dose (*e.g.*, ineffectiveness or safety). Effectiveness was also evaluated by changes in psoriasis severity from baseline to follow-up after treatment with etanercept based on disease severity measured at baseline and follow-up. Disease severity was categorised as "clear" (no evidence of plaques), "mild", "moderate", or "severe" based on the physicians' global subjective assessment of plaque psoriasis severity [18]. Improvement in plaque psoriasis was evaluated in prospective patients who had an available baseline value and at least one disease severity assessment during follow-up. Improvement was defined, based on physicians' global subjective assessment, as patients' disease severity decreasing from either severe or moderate or mild at baseline, to moderate or mild or clear during follow-up.

Continuous variables were reported as means and standard deviations (SD), while categorical variables were summarized as a number and percentage. There were two different types of subpopulations used in the analyses. For descriptive and treatment pattern analyses, patients were grouped as retrospective (first dose prior to 30 days before study enrolment) and prospective (first dose within 30 days prior to or any time after enrolment) patients. Frequencies and incidence rates were used to estimate risk of defined outcomes among two subpopulations: patients with current/recent treatment (active

treatment or last dose within 28 days preceding the event) and patients with previous treatment (no treatment within last 28 days), relative to the event. Evaluations and interpretation were based on point estimates and 95% confidence intervals (CIs). No formal hypothesis testing was performed. All computations were performed using Statistical Analysis Software (SAS)® Version 9.2 or higher.

## Results

### Patient characteristics

Of 72 enrolled patients from 28 sites in eight countries, 37 (51.4%) were males and most patients were White ($n$ = 56; 77.8%). The mean (SD) age was 14.5 (3.3) years at time of enrolment and 7.3 (4.1) years at psoriasis diagnosis. The average duration of disease at baseline was 7.1 years, with prospective patients reporting a shorter average duration of 5.4 years. Of the 72 enrolled patients, 32 were enrolled prospectively and 40 were enrolled retrospectively. At baseline, prospective patients had more moderate (43.8%) or severe (53.1%) disease compared with retrospective patients (37.5% and 25.0%, respectively) *(table 1)*. Psoriatic arthritis was reported in six (8.5%) patients (*table 1*). Of 72 enrolled patients, 29 (40.3%) completed the full follow-up period of five years. Of 43 patients who did not complete five years of follow-up, 20 (27.8%) discontinued early due to the study ending prior to the patient completing five years of follow-up, 11 (15.3%) were lost to follow-up, four (5.6%) moved, four (5.6%) withdrew consent, one (1.4%) participated in a clinical trial, one (1.4%) withdrew due to withdrawal of parental consent, one (1.4%) discontinued due to sponsor decision, and one (1.4%) did not complete the full study period as the site was closed prematurely due to non-responsiveness *(table 2)*. Patients were followed for a mean of 3.8 years. At the time of enrolment, all but one patient (98.6%) had a history of using therapies other than etanercept for treatment of plaque psoriasis, including use of topical steroids (75.0%) and topical vitamin D analogues (48.6%).

**Table 1.** Demographics and baseline clinical characteristics by etanercept status.

| | **All patients ($n$ = 72)** | **Retrospective patients ($n$ = 40)** | **Prospective patients ($n$ = 32)** | **Prospective patients who completed the initial 24 weeks with etanercept ($n$ = 28)** | **Prospective patients who did not complete the initial 24 weeks with etanercept ($n$ = 3)†** |
|---|---|---|---|---|---|
| Age at enrolment (years) | | | | | |
| Mean (SD) | 14.5 (3.3) | 15.4 (3.1) | 13.3 (3.3) | 13.0 (3.2) | 14.6 (3.7) |
| Gender, *n* (%) | | | | | |
| Male | 37 (51.4%) | 22 (55.0%) | 15 (46.9%) | 13 (46.4%) | 2 (66.7%) |
| Female | 35 (48.6%) | 18 (45.0%) | 17 (53.1%) | 15 (53.6%) | 1 (33.3%) |
| Race/ethnicity, *n* (%) | | | | | |
| White or Caucasian | 56 (77.8%) | 28 (70.0%) | 28 (87.5%) | 28 (85.7%) | 3 (100.0%) |
| Black | 1 (1.4%) | 0 (0.0%) | 1 (3.1%) | 1 (3.6%) | 0 (0.0%) |
| Chinese | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Other Asian | 2 (2.8%) | 1 (2.5%) | 1 (3.1%) | 1 (3.6%) | 0 (0.0%) |
| Other | 2 (2.8%) | 1 (2.5%) | 1 (3.1%) | 1 (3.6%) | 0 (0.0%) |
| Not Provided‡ | 11 (15.3%) | 10 (25.0%) | 1 (3.1%) | 1 (3.6%) | 0 (0.0%) |
| Patient age at diagnosis (years) | | | | | |
| Mean (SD) | 7.3 (4.1) | 6.9 (4.2) | 7.9 (4.1) | 7.5 (3.9) | 12.7 (3.0) |
| Duration of disease at baseline (years) | | | | | |
| Mean (SD) | 7.1 (4.5) | 8.6 (4.6) | 5.4 (3.8) | 5.6 (3.8) | 1.8 (0.8) |
| Baseline severity of plaque psoriasis, *n* (%) | | | | | |
| None | 3 (4.2%) | 3 (7.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Mild | 13 (18.1%) | 12 (30.0%) | 1 (3.1%) | 1 (3.3%) | 0 (0.0%) |
| Moderate | 29 (40.3%) | 15 (37.5%) | 14 (43.8%) | 13 (43.3%) | 1 (33.3%) |
| Severe | 27 (37.5%) | 10 (25.0%) | 17 (53.1%) | 16 (53.3%) | 2 (66.7%) |
| Diagnosis of psoriatic arthritis, *n* (%) | | | | | |
| *n* | 71 | 40 | 31 | 27 | 3 |
| Yes | 6 (8.5%) | 4 (10.0%) | 2 (6.5%) | 2 (7.4%) | 0 (0.0%) |
| No | 65 (91.5%) | 36 (90.0%) | 29 (93.5%) | 25 (92.6%) | 3 (100.0%) |
| Missing | 1 | 0 | 1 | 1 | 0 |

*SD: standard deviation.*
*† One patient did not reach 168 days of follow-up and therefore was not included in the analysis of completion/no completion of the initial 24 weeks of etanercept.*
*‡ As per local regulations, race/ethnicity is not provided in France and Portugal.*

## Safety endpoints

There were no events of serious or opportunistic infections, including tuberculosis or malignancy, reported in this study.

## Adverse events

There were 159 treatment-emergent adverse events (TEAEs; defined using Medical Dictionary for Regulatory Activities [MedDRA] v14.0 terminology) reported in 46 (63.9%) of 72 patients with current/recent treatment; of these, 91 were reported as treatment-related TEAEs in 34 (47.2%) patients, among whom, 18 (25.0% of 72) had at least one TEAE leading to permanent treatment discontinuation, and 11 (15.3% of 72) had at least one TEAE leading to dose reduction or temporary treatment discontinuation. TEAEs leading to discontinuation (listed by MedDRA Preferred Term [PT]) included drug ineffectiveness, psoriasis (worsening or exacerbation of psoriasis), anorexia nervosa, pregnancy (pregnancy, puerperium and perinatal conditions with no adverse event), nausea, nasopharyngitis, ear infection, and weight increased. There were 115 TEAEs reported in 32 of 54 (59.3%) patients with previous treatment, and 14 were reported as treatment-related TEAEs in 11 (20.4%) patients.

Crude incidence rates of TEAEs were calculated by exposure status (current/recent treatment or previous exposure), with 66.23 (95% CI: 56.36-77.32) and 98.18 (95% CI: 81.06-117.85) per 100 person-years for current/recent treatment and previous exposure, respectively. Patients with current/recent treatment had a lower risk (relative risk [RR] = 0.68 [95% CI: 0.53-0.86]) of all-cause TEAEs compared to patients with previous exposure. However, patients with current/recent treatment had a higher risk (RR = 3.15 [95% CI: 1.80-5.53]) of treatment-related AEs (AEs deemed attributable to etanercept) compared to patients with previous exposure (*table 3*).

Infections and infestations were the most frequently reported TEAE, with the most frequent being nasopharyngitis followed by influenza. There were 74 events of infections and infestations due to all causalities reported in 31 (43.1%) patients with current/recent etanercept treatment, of which 49 were reported as treatment-related in 19 (26.4%) patients. There were 47 such events reported in 21 (38.9%) patients with previous etanercept exposure, and seven were reported as treatment-related in five (9.3%) patients (*table 3*).

**Table 2.** Patient disposition.

| | All patients (*n*=72) |
|---|---|
| **Patient follow-up, *n* (%)** | |
| Patients who completed 5 years of follow-up[a] | 29 (40.3) |
| Patients discontinuing early (<5 years follow-up)[a] | 43 (59.7) |
| **Reason for early registry discontinuation, *n* (%)** | |
| Withdrawal of patient consent | 4 (5.6) |
| Withdrawal of parent/guardian consent | 1 (1.4) |
| Lost to follow-up | 11 (15.3) |
| Patient death | 0 |
| Other adverse event resulting in discontinuation | 0 |
| Clearing of psoriasis | 0 |
| Other | 26 (36.1) |
| **Duration of patient follow-up (years)** | |
| *n* | 71 |
| Mean (SD) | 3.78 (1.56) |
| Median (range) | 4 (0.13-5.69) |

SD: standard deviation.
[a]Full follow-up period for patients enrolled prior to 1st Oct 2013 was five years while the full follow-up period for patients enrolled after that date was four years.

## Serious adverse events

There were 25 treatment-emergent SAEs reported, including 15 SAEs in 11 (15.3%) patients with current/recent etanercept treatment, with an incidence rate of 6.21 (95% CI: 3.48-10.24) per 100 person-years; whereas 10 such events were reported in seven (13.0%) patients with previous treatment, with an incidence rate of 8.54 (95% CI: 4.09-15.70) per 100 person-years. Skin and subcutaneous tissue disorders (system organ class) were the most frequently reported SAEs, occurring in 10 patients (psoriasis [worsening or exacerbation] [*n*=8], erythema nodosum [*n*=1], and erythrodermic psoriasis [*n*=1]); six (8.3%) patients with current/recent treatment and four (7.4%) with previous treatment. Among 25 SAEs, seven (28.0%) were considered possibly related to etanercept (listed by MedDRA PT: cholesteatoma [*n*=1], hepatic steatosis [*n*=1], flares of psoriasis [*n*=3], and drug ineffectiveness [*n*=2]). The remaining 18 SAEs reported in 13 patients were not considered to be related to etanercept (MedDRA PT: angina pectoris [*n*=1], anorexia nervosa [*n*=1], bronchiolitis [*n*=1], psoriasis [*n*=6], syncope [*n*=1], cholesteatoma [*n*=1], cholelithiasis [*n*=1], paraesthesia [*n*=1], erythrodermic psoriasis [*n*=1], erythema nodosum [*n*=1], chronic tonsillitis [*n*=1], and pregnancy with no adverse event [*n*=2]).

## Effectiveness endpoints

## Patterns of treatment

Patterns of treatment analyses focused only on prospective patients. Effectiveness was not assessed in the retrospective cohort because no baseline measure was available nor could be reliably obtained. Of 32 prospective patients, 28 (87.5%) completed at least 24 weeks of therapy after initiating etanercept, with a mean (SD) duration of 111.5 (88.4) weeks. Five patients required an additional course of etanercept, with a mean (SD) duration of 94.0 (85.9) weeks. Three prospective patients did not complete the initial 24 weeks of treatment, with a mean of 17.5 weeks of treatment and no reports of subsequent etanercept treatment. Among all prospective patients, the mean (SD) cumulative exposure to etanercept was 126.2 (88.4) weeks and the mean (SD) cumulative dose was 4,923.5 (4,142.0) mg. The average

**Table 3.** Treatment-emergent adverse events (all causalities and treatment-related) by treatment status.

| | Current/recent treatment with etanercept (*n* = 72) | Previous exposure to etanercept (*n* = 54) |
|---|---|---|
| **All causalities, *n* (%)** | | |
| Patients with ≥1 TEAE | 46 (63.9%) | 32 (59.3%) |
| Number of TEAEs | 159 | 115 |
| Time at risk (person-years) | 241.6 | 117.1 |
| Incidence rate (per 100 person-years) [95% CI] | 66.23 [56.36-77.32] | 98.18 [81.06-117.85] |
| Relative risk [95% CI] | 0.68 [0.53-0.86] | Ref |
| Patients with ≥1 serious TEAE | 11 (15.3%) | 7 (13.0%) |
| Number of serious TEAEs | 15 | 10 |
| Incidence rate (per 100 person-years) [95% CI] | 6.21 [3.48-10.24] | 8.54 [4.09-15.70] |
| Relative risk [95% CI] | 0.73 [0.33-1.62] | Ref |
| Patients with ≥1 TEAE leading to permanent treatment discontinuation | 24 (33.3%) | 7 (13.0%) |
| Patients with ≥1 TEAE leading to drug reduction or temporary treatment discontinuation | 17 (23.6%) | 2 (3.7%) |
| **Etanercept related, *n* (%)** | | |
| Patients with ≥1 TEAE | 34 (47.2%) | 11 (20.4%) |
| Number of TEAEs | 91 | 14 |
| Time at risk (person-years) | 241.6 | 117.1 |
| Incidence rate (per 100 person-years) [95% CI] | 37.67 [30.33-46.25] | 11.95 [6.53-20.05] |
| Relative risk [95% CI] | 3.15 [1.80-5.53] | Ref |
| Patients with ≥1 serious TEAE | 7 (9.7%) | 0 (0.0%) |
| Number of serious TEAEs | 7 | 0 |
| Patients with ≥1 TEAE leading to permanent treatment discontinuation | 18 (25.0%) | 6 (11.1%) |
| Patients with ≥1 TEAE leading to drug reduction or temporary treatment discontinuation | 11 (15.3%) | 1 (1.9%) |

*CI: confidence interval; Ref: reference population; TEAE: treatment-emergent adverse event.*

number of treatment periods was 1.2 among prospective patients.

Sixteen prospective patients underwent more than one treatment period with other treatments, including four patients with additional systemic therapy and 13 with another systemic biologic (*table 4*). Of these, four (12.5%) prospective patients had concurrent treatment with another biologic during the first course of etanercept, and one (3.1%) had concurrent treatment with another non-biologic systemic treatment during a subsequent course of etanercept.

Of 28 prospective patients with an initial treatment course of at least 24 weeks, seven had treatment still ongoing at the end of follow-up, with no reported dose change or permanent discontinuation. The remaining 21 patients (75.0%) reported at least one of the following: treatment completion, weekly dose change, or permanent discontinuation (*table 5*). Eighteen patients discontinued etanercept with reasons including AE (*n*=1), ineffective treatment (*n*=13), clearing of psoriasis (*n*=2), patient/parent preference or other non-medical reason (*n*=1), or lost to follow-up (*n*=1).

### Changes in disease severity

Among 32 prospective patients, the majority (53.1%) had severe plaque psoriasis at baseline. After treatment with etanercept, 93.8% had a decrease in severity of plaque psoriasis. All 28 patients who completed the initial 24 weeks of etanercept had decreased disease severity during the study, while 66.7% of patients who did not complete the initial 24 weeks reported decreased disease severity after treatment with etanercept. One (3.1%) prospective patient experienced worsening of disease with subsequent improvement during the study when compared with baseline severity.

## Discussion

To our knowledge, this is one of the largest prospective studies with the longest duration of follow-up of patients with paediatric psoriasis who were treated with etanercept in a real-world setting. The primary aim of the study was collection of safety data, in particular SAEs and AEs of special interest in a real-world setting. No opportunistic infections or malignancies, an area of regulatory concern at the start of the study, were reported in this long-term observational study. This is consistent with results of previous studies of etanercept in paediatric patients with plaque psoriasis [19-21] and JIA [22]. When comparing the safety data to that of adalimumab, as reported in the 52-week long-term extension of the

**Table 4.** Etanercept exposure.

| | **All patients (*n* = 72)** | **Prospective patients (*n* = 32)** |
|---|---|---|
| Duration of initial etanercept treatment course (weeks) | | |
| *N* | 72 | 32 |
| Mean (SD) | 116.0 (89.2) | 111.5 (88.4) |
| Duration of subsequent etanercept treatment (weeks) | | |
| *N* | 29 | 5 |
| Mean (SD) | 146.3 (119.9) | 94.9 (85.9) |
| Cumulative exposure to etanercept (weeks)[a] | | |
| *n* | 72 | 32 |
| Mean (SD) | 175.0 (123.0) | 126.2 (88.4) |
| Cumulative dose of etanercept (mg) | | |
| *n* | 71 | 32 |
| Mean (SD) | 9177.6 (15,029.5) | 4923.5 (4142.0) |
| Patients requiring ≥1 treatment period[b] *n* (%) | | |
| Additional etanercept | 28 (38.9%) | 5 (15.6%) |
| *n* | 37 | 16 |
| Additional oral retinoids | 5 (13.5%) | 2 (12.5%) |
| Additional methotrexate | 9 (24.3%) | 3 (18.8%) |
| Additional cyclosporine | 4 (10.8%) | 2 (12.5%) |
| Additional investigational systemic therapy† | 1 (2.7%) | 0 (0.0%) |
| Additional other systemic therapy | 14 (37.8%) | 4 (25.0%) |
| Additional other systemic biologic‡ | 30 (81.1%) | 13 (81.3%) |
| Total number of treatment periods of etanercept reported[c] *n* (%) | | |
| Overall | 114 | 38 |
| Completed | 102 (89.5%) | 34 (89.5%) |
| Incomplete | 12 (10.5%) | 4 (10.5%) |
| Number of treatment periods of etanercept initiated over the course of participation, per patient | | |
| *n* | 72 | 32 |
| Mean (SD) | 1.6 (0.8) | 1.2 (0.5) |

*SD: standard deviation.*

*[a]Cumulative exposure was defined as the period being treated, plus 28 days unless etanercept was re-started within 28 days, in which case the exposure was considered continuous. If etanercept was recorded as continuing the exposure was censored at the data cut-off date, or study discontinuation date, whichever was earlier.*

*[b]The denominator for calculating etanercept percentages is N, as shown in the table header, while for other additional systemic treatment was based on "n", i.e. the number of patients taking such treatments.*

*[c]A complete treatment period was defined as ≥24 weeks of continuous treatment.*

*† Investigational systemic therapies included: BI-655066 (Risankizumab).*

*‡ Other systemic biologic included: COSENTYX® (Secukinumab), HUMIRA® (Adalimumab), STELARA® (Ustekinumab), TALTZ® (Ixekizumab), and TREMFYA® (Guselkumab).*

randomized, double-blind, Phase III trial of adalimumab in children with severe plaque psoriasis [23], the occurrence of TEAEs overall was lower in the current study compared to that of adalimumab (~60% vs. ~80%), with an incidence rate of 66.2 vs. 407.4 per 100 person-years for current/recent treatment with etanercept vs. adalimumab; although the proportion of SAEs reported in the current study was higher than that for adalimumab (~15% vs. ~5%), the incidence rates of SAEs were similar (6.2 vs. 5.8 per 100 person-years for current/recent treatment with etanercept vs. adalimumab). Data for the long-term safety of ustekinumab [24], secukiɵ numab [25] and ixekizumab [26] are similar to that of adalimumab, with a higher percentage of TEAEs and a lower percentage of SAEs reported compared with the current study. Because of the different study populations, designs, methods (an observational registry including both retrospective and prospective patients vs. long-term extension studies of registrational randomized double-blind trials) and follow-up periods, the comparison of results should be interpreted with caution.

Safety data similar to the current study were reported in an open-label extension (OLE) study [19] of the parent 48-week study, which enrolled 182 patients aged 4-17 years with moderate to severe plaque psoriasis, in which 69 completed 264 weeks. Through Week 264 of the OLE study, seven patients reported eight SAEs, which is lower than the frequency of SAEs reported in the current study, PURPOSE, which reported 25 treatment-emergent SAEs in 15 patients. This may be, in part, due to selection criteria for the OLE study by excluding patients who experienced an SAE or clinically significant AE considered related to etanercept in the 48-week parent study. In a retrospective study of 390 children with

**Table 5.** Etanercept dose change or discontinuation among prospective patients.

| Reason for etanercept discontinuation or dose change | Weekly etanercept dose change, *n* | | | | Etanercept permanently discontinued† |
|---|---|---|---|---|---|
| | Dose or frequency increased | Dose or frequency decreased | Same total weekly dose | Type of change not reported | |
| Clearing of psoriasis | - | 2 | - | - | 2 |
| Adverse event | - | 1 | - | - | 1 |
| Treatment ineffective | 2 | - | - | - | 13 |
| Patient/parent preference or other non-medical reason | 1 | - | - | - | 1 |
| Other (reason) | 3 (weight increased, flu, unknown) | - | 1 (unknown) | 1 (unknown) | 1 (lost to follow-up) |

*The table shows the number of events (etanercept dose change or discontinuation) for prospective patients with the initial treatment course of ≥24 weeks. Several events may have been reported per patient (categories are not mutually exclusive).*

*For two events, the intended duration of etanercept treatment was completed with no dose changes (data not shown).*

*† Etanercept discontinuation followed by resumption of treatment was not considered.*

moderate to severe psoriasis undergoing systemic therapy in North America and Europe in 1990-2014, of the 80 patients treated with etanercept, 37 (46%) patients had an AE, 31 (39%) of which were considered medication-related [27]. The most common AE was injection site reaction (19 [24%]), while infection was reported in seven (9%) patients (primarily upper airway infections). This is lower than the 64% of patients reporting AEs with current/recent treatment (47% patients with treatment-related AEs), which is likely due to the active capture of AEs in PURPOSE compared with passive capture in the retrospective study. A 75% improvement in Psoriasis Area and Severity Index (PASI) scores was reported among 60-70% of patients in the OLE study, with 30-40% reporting 90% improvement [19]. The OLE study used severity assessment based on physician global assessment of PASI scores. While PASI scores were not evaluated in PURPOSE, similar improvements were observed through investigator-assessed severity, with 93.8% of prospective patients experiencing a qualitative decrease in the severity of plaque psoriasis after initiating 24 weeks of etanercept treatment. It was notable that some patients received other systemic drugs (particularly biological systemic drugs) after treatment with etanercept.

A multicentre, one-year retrospective study [20] investigating effectiveness, tolerability, and reasons for etanercept discontinuation in a cohort of 23 children and adolescents (≤17 years of age) with moderate to severe plaque psoriasis also reported a reduction in disease severity as measured by the PASI score. At Week 12, 56.5% of patients achieved PASI 75, and 86.9% achieved PASI 50. Among 23 patients, treatment was still ongoing among 15 (65%) patients at the time of data collection, and three (13%) had discontinued due to ineffectiveness. This study reported a lower proportion ($n$=7; 22%) of patients with ongoing treatment at the end of follow-up, with a higher proportion ($n$=13; 41%) of patients discontinuing due to ineffectiveness. This difference may be more likely due to the longer follow-up period in this study. While a relatively high proportion of patients in this study experienced treatment changes and discontinuations, the majority also experienced reduction in disease severity, and any subsequent increases in severity were followed by further reductions in severity. This provides additional evidence of the tolerability and effectiveness of etanercept in this population. The long-term effectiveness of etanercept in patients with paediatric psoriasis appears to be consistent with the adult populations. In the OLE study, approximately 60% of the children and adolescents achieved PASI 75 responses during follow-up for up to five years [19], which is similar to the rate of PASI 75 responses reported in adults receiving etanercept for up to 72 weeks [28].

This study followed paediatric patients with plaque psoriasis under routine clinical practice as determined by their physician. The registry was designed for open enrolment of all paediatric patients undergoing etanercept treatment at the registry sites who met the inclusion criteria. To ensure a naturalistic setting, patient therapy was not decided by study protocol. A clinical decision to prescribe etanercept for psoriasis was made prior to enrolment. However, due to the very low prevalence of paediatric plaque psoriasis, the even smaller proportion treated with etanercept, and that patients were required to agree to participate in a long-term registry, this study is limited by the relatively small sample size and cumulative patient-years of etanercept exposure, at 242 years. The demographics of the enrolled population appear broadly generalizable to the overall paediatric psoriasis population in the USA and Europe, with a majority of patients being White and a similar proportion of male and female patients [2]. The registry included a sub-cohort of patients who initiated etanercept prior to registry enrolment, which may have created a potential bias as these patients were substantially different from patients prescribed etanercept at the same time but later discontinued due to poor tolerance, AEs, or ineffectiveness. This could have led to underestimation of the risk of developing an AE in the retrospective population. To minimize this bias, retrospective and prospective patients were analysed separately.

In summary, in this long-term study conducted in a real-world setting of paediatric patients with plaque psoriasis receiving treatment with etanercept, no serious or opportunistic infections or malignancies were observed. There were 25 treatment-emergent SAEs, including seven that were considered possibly related to etanercept. The descriptive effectiveness data suggest that the majority of the prospective patients experienced a decrease in the severity of plaque psoriasis after treatment with etanercept. The results from this real-world registry study are consistent with the known safety and efficacy profile of etanercept in paediatric patients with plaque psoriasis and, therefore, do not provide new information to warrant a change to the benefit-risk profile of etanercept use in this patient population. Taking the known limitations of naturalistic settings into consideration, the findings of this study add to the evidence regarding long-term use among the paediatric plaque psoriasis population, and results from the prospective patients are generalizable to patients initiating treatment with etanercept.

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***Availability of data and material:*** *upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.*

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***Conflicts of interest:*** *Yun Gu is an employee and shareholder of Pfizer, one of the manufacturers of etanercept. Emma Brinkley, Sara Colli, and Joan Largent are employed by IQVIA, which received funding from Pfizer for the study and the development of the manuscript. Rachel E. Sobel was an employee of Pfizer at the time of the study and manuscript development and is a current shareholder of Pfizer, one of the manufacturers of etanercept. Diamant Thaçi reports personal fees as lecturer/consultant/scientific advisory board member from AbbVie, Almirall, Amgen, Asana Biosciences, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Janssen-Cilag, Kyowa Kirin, Leo Pharma, Eli Lilly, Novartis, Regeneron, Sandoz, Sanofi-Aventis, Pfizer, and UCB, and grants from AbbVie, Celgene, Leo Pharma, and Novartis, during the conduct of the study. Mona Ståhle has received grants from/was involved in clinical trials for AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Leo Pharma, and Pfizer. She served as a consultant for AbbVie, Eli Lilly, Janssen, Leo Pharma, Novartis, Pfizer, and UCB; fees were paid directly to the institution. Zsuzsanna Szalai has no conflicts to declare. Jean-Philippe Lacour has received grants/research support as an investigator and honoraria, advisory board member or consulting fees from AbbVie, BMS, Boehringer Ingelheim, Celgene, Dermira, Galderma, Janssen, Eli Lilly and Company, Merck, Novartis, Regeneron, Roche, and Sanofi. Marieke Seyger has received grants from/was involved in clinical trials for AbbVie, Celgene, Eli Lilly, Janssen, Leo Pharma, and Pfizer, and served as a consultant for AbbVie, Eli Lilly, Janssen, Leo Pharma, and Pfizer.*

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