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Clinical science

Ten-year safety and clinical benefit from open-label etanercept treatment in children and young adults with juvenile idiopathic arthritis

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Abstract

Objectives: CLIPPER2 was an 8-year, open-label extension of the phase 3b, 2-year CLIPPER study on the safety and efficacy of etanercept in patients with JIA, categorized as extended oligoarticular arthritis (eoJIA), enthesitis-related arthritis (ERA) or PsA.

Methods: Participants with eoJIA (2–17 years old), ERA or PsA (each 12–17 years old) who received ≥1 etanercept dose (0.8 mg/kg weekly; maximum 50 mg) in CLIPPER could enter CLIPPER2. Primary end point was occurrence of malignancy. Efficacy assessments included proportions achieving JIA ACR 30/50/70/90/100 criteria and ACR inactive disease criteria, and clinical remission (ACR criteria) or Juvenile Arthritis DAS (JADAS) ≤1.

Results: Overall, 109/127 (86%) CLIPPER participants entered CLIPPER2 [$n=55$ eoJIA, $n=31$ ERA, $n=23$ PsA; 99 (78%) on active treatment]; 84 (66%) completed 120 months' follow-up [32 (25%) on active treatment]. One malignancy (Hodgkin's disease in 18-year-old patient with eoJIA treated with methotrexate for 8 years) was reported; there were no cases of active tuberculosis or deaths. Numbers and incidence rates (events per 100 patient-years) of TEAEs (excluding infections/ISRs) decreased from 193 (173.81) in Year 1 to 9 (27.15) in Year 10; TE infections and serious infections also decreased. Over 45% of participants ($n=127$) achieved JIA ACR50 responses from Month 2 onwards; 42 (33%) and 34 (27%) participants achieved JADAS and ACR clinical remission, respectively.

Conclusions: Etanercept treatment up to 10 years was well tolerated, consistent with the known safety profile, with durable response in the participants still on active treatment. The benefit–risk assessment of etanercept in these JIA categories remains favourable.

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Rheumatology key messages

- CLIPPER trials provide ≤10 years of data on etanercept in patients with juvenile idiopathic arthritis.
- One malignancy (Hodgkin's disease) was reported; no cases of active tuberculosis or deaths occurred.
- The benefit–risk assessment of etanercept in juvenile patients was positive.

Introduction

JIA, defined as persistent (>6 weeks) arthritis of unknown aetiology with onset before age 16 years, refers to a heterogeneous group of diseases classified by the International League of Associations for Rheumatology into seven mutually exclusive categories: systemic arthritis, oligoarthritis, RF-negative polyarthritis, RF-positive polyarthritis, PsA, enthesitis-related arthritis (ERA) and undifferentiated JIA [1]. Disease heterogeneity is based on different genetic susceptibility, immunopathogenesis, age at onset, number and distribution of affected joints, and presence of extra-articular manifestations [2, 3].

While treatment algorithms differ across JIA categories, initial pharmacologic treatment of JIA typically involves NSAIDs and/or intraarticular glucocorticoid injection, followed by conventional synthetic DMARDs (csDMARDs) and/or intraarticular glucocorticoids [4–7]. If the response to the initial csDMARD is considered clinically inadequate for the treatment of JIA, or there is intolerance or side effects to csDMARDs, then use of a biologic DMARD (bDMARD)—such as a TNF alpha (TNFα) inhibitor, anti-IL6, or abatacept—is a possible treatment option as recommended according to the specific JIA category [4–7]. Despite substantial progress in the treatment of JIA over recent years, JIA remains a chronic condition for many affected children, and a significant portion of patients require treatment into adulthood [8–10]. It is important to understand the long-term safety and clinical benefit profile when treating young patients with biologics.

Etanercept is a TNFα inhibitor that demonstrated efficacy and was well tolerated in patients with polyarticular JIA in a randomized, placebo-controlled trial, which included a withdrawal arm [11]. Durable responses and an acceptable safety profile were observed during an open-label extension with up to 8 years' follow-up [12].

There remains a need for long-term efficacy and safety data with etanercept in different JIA categories. CLIPPER was a phase 3b single-arm trial of the efficacy and safety of open-label etanercept in patients with eoJIA, ERA or PsA [13, 14]. CLIPPER2 was an open-label extension with an additional 8 years of follow-up (10 years in total). Interim data after 6 years (2 years in CLIPPER and 4 years in CLIPPER2) have been reported previously [15]. We report the end-of-study safety and efficacy results from CLIPPER2, after a total of up to 10 years of treatment with etanercept.

Methods

Study design and participants

The study design and participant inclusion criteria for CLIPPER/CLIPPER2 have been described previously and are summarized in Supplementary Fig. S1, available at *Rheumatology* online [13–15].

The CLIPPER parent study (NCT00962741) was a 24-month, phase 3b, open-label, single-arm study of etanercept conducted at 38 centres in 19 member countries of PRINTO [16]. Participants with eoJIA (aged 2–17 years), ERA (aged 12–17 years) or PsA (aged 12–17 years) enrolled to receive etanercept 0.8 mg/kg subcutaneously once weekly (maximum dose: 50 mg/week).

CLIPPER2 (NCT01421069) was an 8-year, open-label extension study. All participants who received ≥1 dose of etanercept and completed ∼96 weeks' participation in CLIPPER could participate in CLIPPER2. CLIPPER2 comprised three periods: active treatment, withdrawal/re-treatment and observation (Supplementary Fig. S1, available at *Rheumatology* online). The primary end point in CLIPPER2 was occurrence of malignancy. The long-term safety profile, including occurrence of serious AEs, serious infections and medically important infections, as well as the long-term efficacy of etanercept and impact on health outcomes were assessed in secondary endpoints.

The study was approved by the relevant regulatory bodies of each country and institution and was conducted in compliance with the ethical principles originating in the Declaration of Helsinki, all International Council for Harmonisation Good Clinical Practice Guidelines, and local regulatory requirements. All participants or their parents/guardians provided informed written consent prior to participating in any study activities.

Assessments

During the active treatment and withdrawal/re-treatment periods, safety assessments included physical examination, vital signs (temperature, blood pressure, heart rate), height and weight, adverse events (AEs) and injection site reaction (ISR), clinical laboratory evaluations (blood chemistry and urinalysis) and malignancy. All AEs and serious AEs (SAEs) as per MedDRA version 23.1, including infections, serious infections, medically important infections, infections considered preventable by vaccinations, ISRs and malignancies, were reported for the duration of the active treatment period, the withdrawal/re-treatment period, and for 30 days after the last dose of active treatment. SAEs, including serious infections, malignancies and medically important infections, were also reported during the observational period.

Efficacy endpoints were assessed through Month 96 of CLIPPER2 during the active treatment and withdrawal/re-treatment periods, including the six JIA ACR core set of measures [17]: the Patient/Parent Global Assessment (PtGA) [18], the Physician's Global Assessment (PGA) of disease activity

[18], both with a 21-circle visual analogue scale (VAS) [18], the number of active joints and the number of joints with limited range of motion, laboratory measures of inflammation (levels of CRP), and the cross-culturally adapted version of the Childhood HAQ (CHAQ; completed by the participant's parent/guardian for participants <18 years old at the time of assessment) or the HAQ; completed by the participant directly for participants ≥18 years of age at the time of the assessment [19]. Additional measures included pain assessment (21-circle VAS, from 0 = no pain to 10 = very severe pain) and duration of morning stiffness. For participants with ERA, overall/nocturnal back pain, and the BASMI, and for participants with PsA the percent body surface area affected by psoriasis (palm method) and PGA of psoriasis, were also recorded. Response to treatment was assessed by composite measures as secondary efficacy endpoints, including JIA ACR 30/50/70/90/100 response criteria [17], defined as ≥30% (and 50%, 70%, 90%, 100%, respectively) improvement from baseline in at least three of the following six JIA core set measures, with no >1 remaining variable worsening by >30%: PGA of disease activity, PtGA, CHAQ/HAQ, number of joints with active arthritis, number of joints with limited range of motion, and CRP levels. Clinically inactive disease (CID) was defined as follows per JIA ACR Wallace criteria [20]: no joints with active arthritis, no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA, no active uveitis, CRP level within normal limits (or not attributable to JIA if elevated), best possible PGA, and duration of morning stiffness ≤15 min. Juvenile Arthritis DAS (JADAS) [21] was assessed with 73-joint counts (Supplementary Fig. S2, available at *Rheumatology* online) using four components (PGA of disease activity, PtGA, number of joints with active arthritis and CRP) [22]. Disease activity was defined according to JADAS73 score cut-offs [22] as high disease activity (>17.0), moderate disease activity (6.1–17.0), low disease activity (2.8–6.0) or CID (≤2.7). Exploratory efficacy endpoints included (i) time to flare following etanercept withdrawal (defined as ≥30% worsening in at least three of the six JIA ACR components, with ≥30% improvement in not >1 of the remaining six components and a minimum of two active joints) [23], and (ii) time from withdrawal to re-treatment with etanercept.

Statistical analysis

All efficacy and safety analyses were based on the modified intention-to-treat (mITT) population, defined as all participants who received at least one dose of etanercept, unless mentioned otherwise. Safety, including malignancies (primary end point) and other treatment-emergent adverse events (TEAEs), was assessed from CLIPPER baseline to Month 96 in CLIPPER2 (referred to as Month 120 here). For participants in the observational period, safety was assessed as SAEs, malignancies and medically important infections only. TEAEs were summarized as number of events, percentages of participants with events, and adjusted rates per 100 patient-years exposure (EP100PY) to etanercept with corresponding 95% confidence intervals (CIs).

Secondary efficacy endpoints were analysed during the active treatment period and the withdrawal/re-treatment period. Descriptive statistics were determined for each end point at all timepoints during the study, including frequency, percentages, and 95% CI for categorical endpoints, and number of observations, mean, standard deviations, median, range, and 95% CI for the mean (raw data and change from baseline) for continuous endpoints. For all change from baseline analyses, baseline refers to start of the parent (CLIPPER) study. Hybrid method was used for missing data imputation where indicated.

The sample size in CLIPPER2 was not based on efficacy considerations; rather, all eligible participants who completed or discontinued CLIPPER were invited to participate in CLIPPER2 (anticipated enrolment was ∼100 participants).

Results

Participants

The CLIPPER parent study was conducted between September 2009 and January 2013. CLIPPER2 was initiated on 10 October 2011 and the last participant visit was on 4 February 2021.

Of 127 participants who received ≥1 dose study drug in CLIPPER, 109 (86%) enrolled in CLIPPER2 (eoJIA $n = 55$; ERA $n = 31$; PsA $n = 23$) and 84 participants (66%) completed the study at Month 120, 32 (25%) of whom were actively taking etanercept. A total of 43 participants (34%) permanently discontinued from the study, including 18 (14%) who withdrew during CLIPPER and 25 (20%) who withdrew during CLIPPER2. Details regarding participant disposition in CLIPPER/CLIPPER2 are shown in Fig. 1. The analysis set for the optional withdrawal period (see Supplementary Fig. S1, available at *Rheumatology* online, for entering criteria) included 30 (23.6%) participants (eoJIA $n = 16$; ERA $n = 9$; PsA $n = 5$) and the re-treatment analysis set included 13 (10.2%) participants (eoJIA $n = 8$; ERA $n = 2$; PsA $n = 3$).

Participant demographic and disease characteristics at the baseline of CLIPPER [14] and CLIPPER2 [15] have been reported previously and are summarized in Supplementary Table S1, available at *Rheumatology* online. Participants enrolled in CLIPPER2 were similar at baseline to CLIPPER participants. Overall, 56.7% of CLIPPER participants were female (eoJIA 68.3% and PsA 79.3%), while most participants with ERA (78.9%) were male. The mean age (S.D.) at the start of CLIPPER was 11.7 (4.5) years overall and 8.6, 14.5 and 14.5 years among participants with eoJIA, ERA and PsA, respectively. Most ($n = 90$) participants who continued into CLIPPER2 were <18 years of age at the start of CLIPPER2, all continuing participants with ERA or PsA were >12 years of age, and 32 participants with eoJIA were <12 years of age.

At CLIPPER baseline, the median disease duration was 26.8 (26.4) months. Most (85.8%) participants were receiving a concomitant DMARD, most commonly methotrexate (67.7%). Among 27 participants who remained on etanercept treatment for 120 months, 13 received concomitant DMARDs (11 received methotrexate, two received sulfasalazine) until the end of the study.

Safety

The total combined etanercept exposure in CLIPPER/CLIPPER2 was 683.2 patient-years. There was one case of malignancy (primary end point) during CLIPPER/CLIPPER2. As described previously [15], this was a case of Hodgkin's disease in an 18-year-old participant with eoJIA in Year 3 treated with etanercept for 27 months and methotrexate for 8 years who subsequently discontinued from the study. No

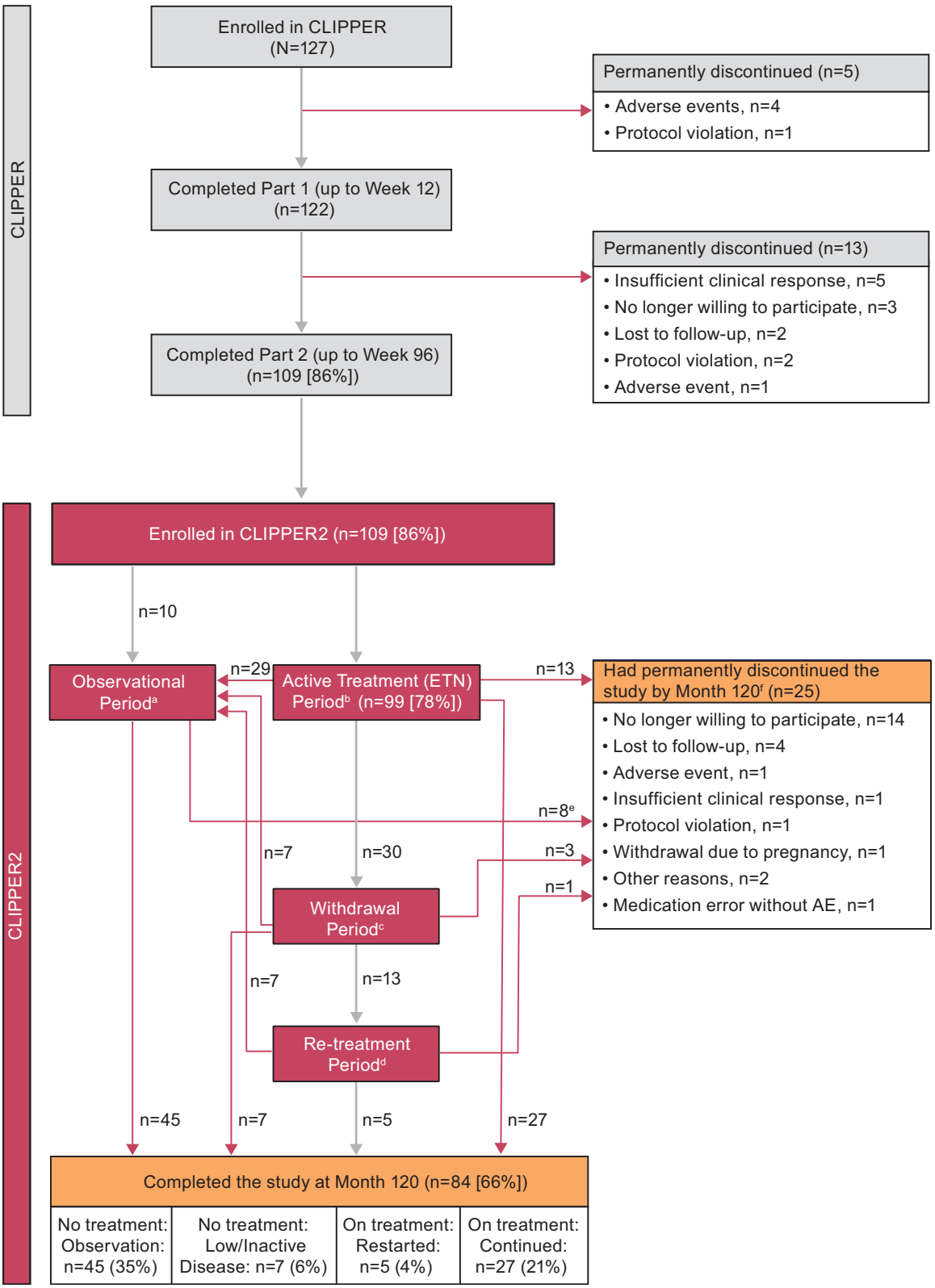

Figure 1. Study design and participant disposition in CLIPPER and CLIPPER2. Figure was adapted based on Foeldvari *et al.* [15] 'Etanercept treatment for extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis, or psoriatic arthritis: 6-year efficacy and safety data from an open-label trial' by Foeldvari I *et al.* is licenced under CC BY 4.0. [a]Patients who stopped treatment but were still followed in CLIPPER2. [b]Patients actively receiving open-label treatment with ETN. [c]Patients who either met the 2011 Wallace definition for clinically inactive disease for ≥6 months on ETN or who, in the investigator's clinical judgement, had a good clinical response and would benefit from treatment withdrawal. [d]Patients in the Withdrawal Period who required re-treatment per the investigator's clinical judgement and re-started ETN. [e]Includes two patients who entered the Observational Period directly from CLIPPER, plus six patients who entered the Observational Period from another treatment phase. [f]Patients who were no longer being followed as part of CLIPPER or CLIPPER2. AE: adverse event; ETN: etanercept

Table 1. Safety summary of etanercept treatment to Month 120

	eoJIA ($n=60$)	ERA ($n=38$)	PsA ($n=29$)	Total ($n=127$)
Exposure, patient-years	313.7	207.0	162. 6	683.2
TEAEs[a]	269 (85.8)	176 (85.0)	114 (70.1)	559 (81.8)
TE serious AEs[a]	16 (5.1)	17 (8.2)	7 (4.3)	40 (5.9)
TE ISRs	23 (7.3)	29 (14.0)	12 (7.4)	64 (9.4)
TE infections	418 (133.3)	99 (47.8)	155 (95.3)	672 (98.4)
TE serious infections	5 (1.6)	4 (1.9)	5 (3.1)	14 (2.1)
Opportunistic infections[b]	0	1 (0.5)	1 (0.6)	2 (0.3)
TEAEs causing withdrawal[a]	7 (2.2)	9 (4.4)	2 (1.2)	18 (2.6)
TE infections causing withdrawal	2 (0.6)	0	1 (0.6)	3 (0.4)

Data are shown as N (EP100PY) unless stated otherwise. Based on mITT population.[c]
[a] Excluding infections/ISRs.
[b] Both herpes zoster.
[c] While on active etanercept treatment or within 30 days of last dose.
eoJIA: extended oligoarticular JIA; ERA: enthesitis-related arthritis; EXP: exposure to etanercept; ISR: injection site reaction; mITT: modified intention-to-treat; PY: patient-years; TE: treatment emergent; TEAE: treatment-emergent adverse event.

other cases of malignancy were reported through the end of CLIPPER2, and no malignancies were reported during the withdrawal/re-treatment or observational periods.

A summary of the etanercept treatment safety profile from CLIPPER baseline through end of CLIPPER2, including the incidence of TEAEs and infections, and participant withdrawals owing to these, is shown in Table 1. The number and incidence rates of TEAEs (excluding infections and ISRs) and TE infections decreased over time while serious TEAS and TE serious infections remained low throughout the study (Fig. 2). No increase in the infection rate was observed with ongoing and prolonged exposure to etanercept.

The most frequently reported TEAEs were headache [28 TEAEs in 17 participants (4.10 EP100PY)], arthralgia [24 TEAEs in 16 participants (3.51)], pyrexia [21 TEAEs in 14 participants (3.07)], diarrhoea [14 TEAEs in 12 participants (2.05)] and leukopoenia [12 TEAEs in nine participants (1.76)] (Table 2).

Forty treatment-emergent SAEs (5.85 EP100PY) were reported by 30 participants (23.6%), excluding infections/ISRs (Supplementary Table S2, available at *Rheumatology* online). All occurred at a rate of ≤3 events each, and only Crohn's disease (eoJIA $n=2$; ERA $n=1$), juvenile arthritis (ERA $n=2$) and psoriasis (PsA $n=2$) were reported in >1 participant.

A total of 672 treatment-emergent (TE) infections were reported in 108 participants (85.0%) in the overall population, including 418 (133.3 EP100PY) TE infections in 53 participants with eoJIA, 99 (47.8 EP100PY) in 31 participants with ERA, and 155 (95.3 EP100PY) in 24 participants with PsA. The most common TE infections were upper respiratory tract infections [168 events (24.59 EP100PY)], pharyngitis [104 (15.22)], bronchitis [33 (4.83)], and gastroenteritis [32 (4.68)] (Table 2). Most TE infections were not considered study drug-related and were of mild or moderate severity. Study drug-related TE infections were reported in 29 participants, including severe infections of appendicitis and peritonitis in one participant with eoJIA, and septic shock in another participant with eoJIA. The rate of TE serious infections was low, with 14 events reported by 11 participants (8.7%; 2.05 EP100PY; Table 2). Only gastroenteritis was reported more than once during the study ($n=2$; 0.29 EP100PY), with one case during Year 1 and another during Year 2 of CLIPPER in two different participants with eoJIA. Two opportunistic infections were reported in Year 1 of CLIPPER. Both were cases of herpes

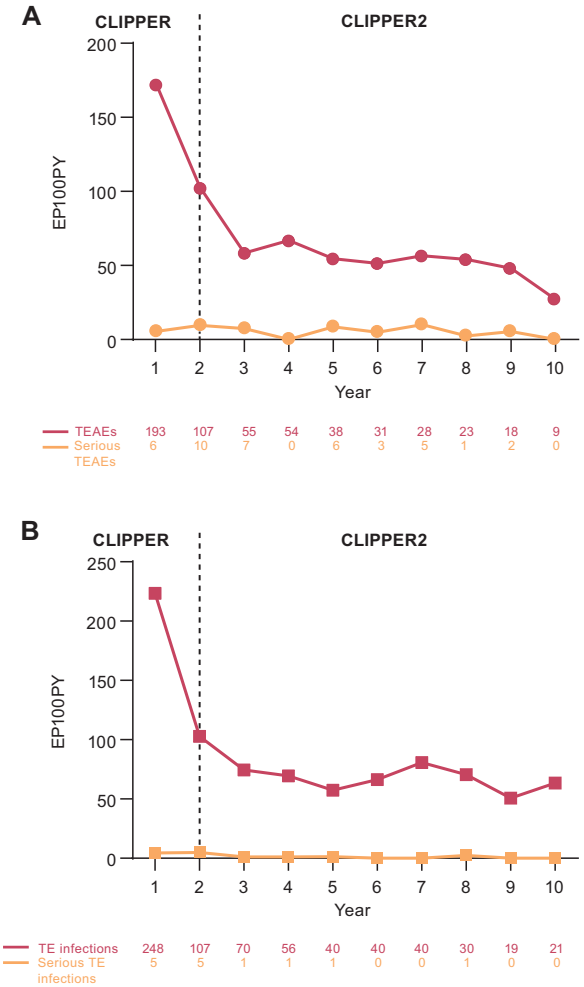

Figure 2. Incidence of (**A**) TEAEs[a] and (**B**) TE Infections in CLIPPER/CLIPPER2 by study year. Data are shown as events per 100 patient-years of follow-up. [a]Excluding infections/injection site reactions. EP100PY: events per 100 patient-years; TE: treatment emergent; TEAE: treatment-emergent adverse event

zoster in one participant with ERA and one participant with PsA. No cases of active tuberculosis or other opportunistic infections were reported during CLIPPER/CLIPPER2.

Sixteen participants (12.6%) reported ≥1 ISR, none of which were serious. Overall, 64 TE ISRs were reported (9.37

Table 2. Summary of all causality TEAEs[a], TE infections[b] and TE serious infections[c] to Month 120

	eoJIA ($n=60$)	ERA ($n=38$)	PsA ($n=29$)	Total ($n=127$)
TEAEs[d], *n* (EP100PY)				
Headache	12 (3.8)	5 (2.4)	11 (6.8)	28 (4.1)
Arthralgia	11 (3.5)	8 (3.9)	5 (3.1)	24 (3.5)
Pyrexia	11 (3.5)	3 (1.5)	7 (4.3)	21 (3.1)
Diarrhea	5 (1.6)	7 (3.4)	2 (1.2)	14 (2.1)
Leukopenia	9 (2.9)	2 (1.0)	1 (0.6)	12 (1.8)
Nausea	7 (2.2)	2 (1.0)	1 (0.6)	10 (1.5)
Vomiting	8 (2.6)	1 (0.5)	1 (0.6)	10 (1.5)
Joint effusion	8 (2.6)	0	0	8 (1.2)
Cough	7 (2.2)	1 (0.5)	0	8 (1.2)
Ligament sprain	6 (1.9)	1 (0.5)	0	7 (1.0)
TE infections, *n* (EP100PY)				
Upper respiratory tract infection	110 (35.1)	19 (9.2)	39 (24.0)	168 (24.6)
Pharyngitis	54 (17.2)	23 (11.1)	27 (16.6)	104 (15.2)
Bronchitis	20 (6.4)	7 (3.4)	6 (3.7)	33 (4.8)
Gastroenteritis	19 (6.1)	5 (2.4)	8 (4.9)	32 (4.7)
Tonsillitis	20 (6.4)	5 (2.4)	3 (1.9)	28 (4.1)
Ear infection	20 (6.4)	0	2 (1.2)	22 (3.2)
Nasopharyngitis	15 (4.8)	3 (1.5)	4 (2.5)	22 (3.2)
Influenza-like illness	11 (3.5)	0	3 (1.9)	14 (2.1)
Oral herpes	12 (3.8)	2 (1.0)	0	14 (2.1)
Influenza	11 (3.5)	1 (0.5)	1 (0.6)	13 (1.9)
TE serious infections, *n* (EP100PY)				
Infections and infestations	5 (1.59)	4 (1.93)	5 (3.08)	14 (2.05)
Acute tonsillitis	0	0	1 (0.62)	1 (0.15)
Anal abscess	0	1 (0.48)	0	1 (0.15)
Bronchopneumonia	1 (0.32)	0	0	1 (0.15)
Gastroenteritis	2 (0.64)	0	0	2 (0.29)
Gastrointestinal infection	0	0	1 (0.62)	1 (0.15)
Helicobacter gastritis	0	1 (0.48)	0	1 (0.15)
Influenza	0	0	1 (0.62)	1 (0.15)
Peritonitis	1 (0.32)	0	0	1 (0.15)
Pharyngitis	0	1 (0.48)	0	1 (0.15)
Pyelocystitis	0	0	1 (0.62)	1 (0.15)
Sepsis	1 (0.32)	0	0	1 (0.15)
Urinary tract infection	0	0	1 (0.62)	1 (0.15)
Viral infection	0	1 (0.48)	0	1 (0.15)

Based on mITT population.[e]
[a] Preferred term >5 events in any JIA category.
[b] Preferred term >10 events in any JIA category.
[c] All serious TE events by system organ class and preferred term.
[d] Excluding infections/ISRs.
[e] While on active etanercept treatment or within 30 days of last dose.
AE: adverse event; eoJIA: extended oligoarticular JIA; EP100PY: events per 100 patient-years; ERA: enthesitis-related arthritis; FAS: full analysis set; ISR: injection site reaction; mITT: modified intention-to-treat; TE: treatment emergent; TEAE: treatment-emergent adverse event.

EP100PYs), corresponding to 142 ISR symptoms (20.78 EP100PY) including itching, redness, swelling and pain. Redness was the most frequent ISR symptom (8.64 EP100Y). No ISRs were reported after Year 3.

Seventeen (2.49 EP100PY) TE autoimmune disorders were reported in 14 participants, including 14 (2.05 EP100PY) TEAEs each of uveitis (eoJIA $n=4$; ERA $n=6$; PsA $n=4$) in 13 participants and three (0.44 EP100PY) TEAEs of Crohn's disease (in three participants). Four TEAEs of uveitis led to etanercept withdrawal: two in participants with eoJIA in Year 6 (one case was considered an SAE), one SAE in a participant with eoJIA in Year 8 and one nonserious AE in a participant with ERA in Year 9. The TEAEs of Crohn's disease were reported in two participants with ERA, in Year 1 and Year 6, and one participant with eoJIA, in Year 5. All were considered SAEs and led to withdrawal of study treatment.

Fourteen participants (11.0%) discontinued study treatment due to AEs (excluding infections and ISRs) (Supplementary Table S3, available at *Rheumatology* online). AEs that resulted in etanercept withdrawal included Crohn's disease reported in three (2.4%) participants, and uveitis each reported in four (3.1%) participants, as described above; all other TEAEs resulting in etanercept withdrawal were reported in one (0.8%) participant each, including Hodgkin's disease. Three participants (2.4%) discontinued treatment due to TE infections (one case each of bronchopneumonia, pyelocystitis, and sepsis) (Supplementary Table S3, available at *Rheumatology* online).

No deaths were reported during the study. Review of clinical safety laboratory results did not reveal any unexpected safety signals (data not shown).

Efficacy

JIA ACR 30, 50, 70 and 100 response rates in the mITT population over 10 years are presented in Fig. 3. While response rates remained largely stable or increased during CLIPPER, a steady decline was observed during CLIPPER2. However, most (>95%) participants with JIA who continued on

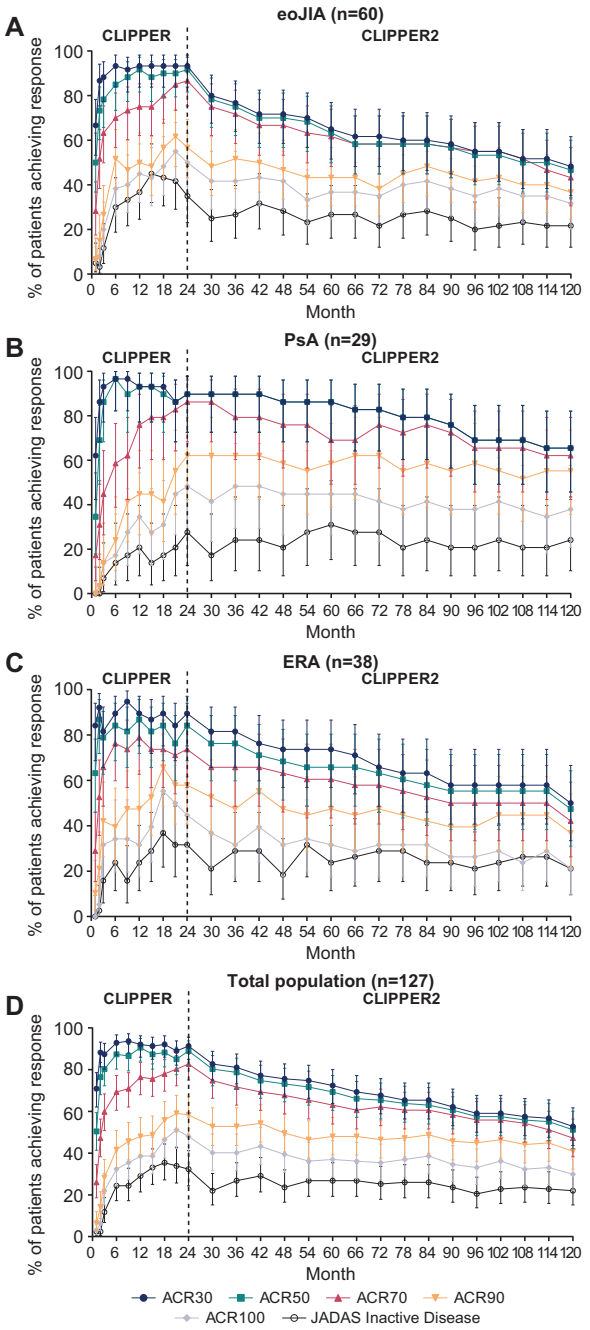

Figure 3. JIA ACR and JADAS inactive disease response rates. (**A**) eoJIA, (**B**) PsA, (**C**) ERA and (**D**) total population. Data shown as mean (95% CI). Based on mITT population using hybrid imputation methods. ACR 30/50/70/90/100: American College of Rheumatology 30/50/70/90/100 criteria; eoJIA: extended oligoarticular JIA; ERA: enthesitis-related arthritis; JADAS: Juvenile Arthritis DAS; mITT: modified intention-to-treat

etanercept achieved JIA ACR 30 response at all study time points during CLIPPER2 based on observed cases (OC) analysis (Supplementary Fig. S3, available at *Rheumatology* online). All but four participants on active treatment achieved JIA ACR 50 and 70 at all timepoints from Month 54 through Month 96 of CLIPPER2.

Fluctuations in the proportion of participants achieving CID (JIA ACR Wallace criteria) were observed over time and across JIA categories (data not shown). At Month 120, 22.0% of participants [n/*N* = 28/127; eoJIA 21.7% (13/60); ERA 21.1% (8/38); PsA 24.1% (7/29)] achieved CID. Remission for 12 consecutive months was achieved in 34 of 127 participants (26.8%) based on ACR Wallace criteria and in 42 of 127 (33.1%) participants according to JADAS criteria, with similar proportions observed across the JIA categories.

Decreases in JADAS disease activity (OC analysis) from CLIPPER baseline were observed during the 2-year parent study, and mean JADAS remained below CLIPPER baseline throughout CLIPPER2, with some fluctuations across time points and JIA categories (Fig. 4). The observed mean (S.D.) JADAS was 2.05 (2.55) overall and 2.74 (3.35), 1.69 (1.62) and 1.20 (1.64) in the eoJIA, ERA and PsA categories, respectively, at Month 96 of CLIPPER2, representing mean decreases from CLIPPER baseline of 89.2% overall and 86.0%, 89.3% and 94.9% in the eoJIA, ERA and PsA categories.

Similarly, the improvements from baseline in mean scores for individual components of the JIA ACR assessments and patient-reported outcomes observed at Month 24 of CLIPPER were maintained through CLIPPER2 (Supplementary Table S4, available at *Rheumatology* online).

Mean CRP levels generally remained below parent study baseline levels across JIA categories for up to 10 years (Supplementary Fig. S4, available at *Rheumatology* online).

The proportion of participants with improvements in CHAQ scores (reduction >0.188) from CLIPPER baseline increased over time, reaching 100% from Month 54 onwards in CLIPPER2; however, participant numbers were low at later timepoints (Supplementary Fig. S5, available at *Rheumatology* online).

Among participants with ERA, overall and nocturnal back pain scores (by VAS) remained lower at all time points during CLIPPER2 compared with CLIPPER baseline, and mean BASMI total scores generally decreased with time (Supplementary Fig. S6, available at *Rheumatology* online). Among participants with PsA, the percentage of body surface area affected by psoriasis decreased across study timepoints, with a mean of 0.8% at Month 96 (Supplementary Fig. S7, available at *Rheumatology* online). The mean score for PGA of psoriasis remained below CLIPPER baseline throughout the study.

Overall, 30 participants (23.6%) entered the withdrawal period, of whom 17 (57%) were reported to have a flare after etanercept withdrawal. The median time to flare from etanercept withdrawal (Kaplan–Meier analysis) was 190 (95% CI: 90, NA) days. Thirteen participants (10.2%) started re-treatment after etanercept withdrawal, after a median of 274 (95% CI: 106, NA) days.

Discussion

We report the safety and efficacy of etanercept in participants with JIA with eoJIA, ERA and PsA after up to 10 years of continuous treatment in CLIPPER/CLIPPER2. Measures of disease activity and health outcomes remained relatively stable throughout the 10-year study across the JIA categories, suggesting continued clinical benefit.

Treatment with etanercept was well tolerated and consistent with its known safety profile. There were no unexpected safety findings or new safety signals throughout CLIPPER/CLIPPER2. The rates of TEAEs, TE infections and TE serious infections generally declined over time. There was one

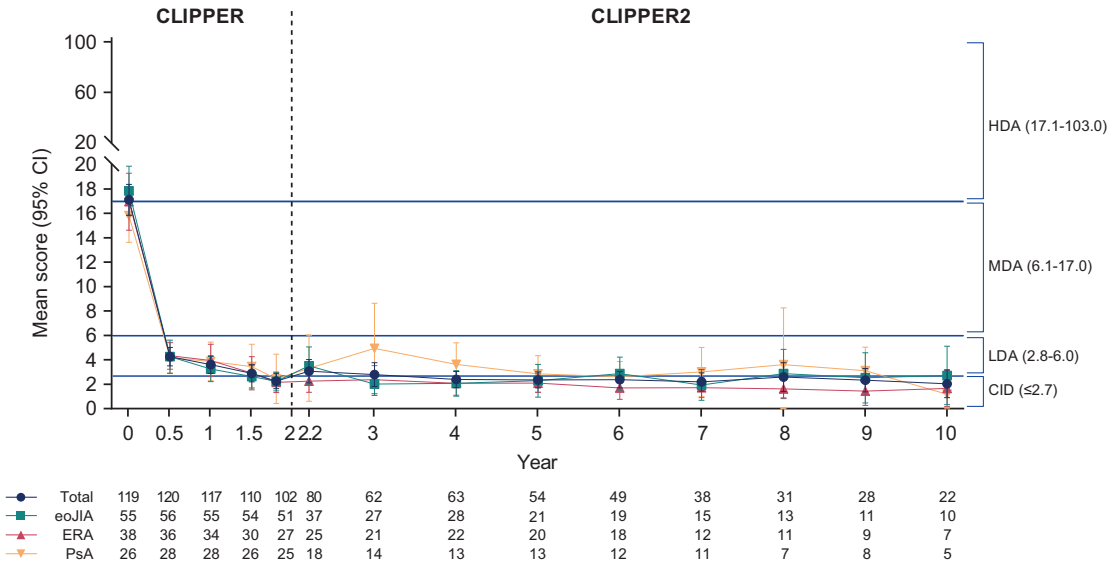

Figure 4. JADAS 73 score by visit[a]. Based on observed cases. [a]Disease activity based on cut-off values of the JADAS score [22]. Maximum possible score: 103. CID: clinically inactive disease; eoJIA: extended oligoarticular JIA; ERA: enthesitis-related arthritis; HDA: high disease activity; JADAS: Juvenile Arthritis DAS; LDA: low disease activity; MDA: moderate disease activity

malignancy reported, a Hodgkin's lymphoma that has been described in detail previously [15]. The relationship of this case to etanercept and/or methotrexate cannot be ruled out. The reported incidence rate of malignancy among participants with JIA in the absence of exposure to methotrexate, TNF inhibitors or other immunomodulatory agents is 105.8 (95% CI: 47.5, 235.5) per 100 000 patient-years [24]. The incidence rate of malignancies observed here (i.e. one case during 683.2 patient-years exposure, or ∼146 per 100 000 patient-years) is within the range observed for patients with JIA not exposed to TNF inhibitors. Autoimmune disorders included three occurrences of Crohn's disease (0.44 EP100Y) and 14 occurrences of uveitis (2.05 EP100Y).

Results from CLIPPER2 are consistent with a previous clinical trial of etanercept in participants with polyarticular juvenile rheumatoid arthritis, in which etanercept was well tolerated with durable responses observed through up to 8 years of treatment [12]. Similar results were also observed in an open-label, 3-year safety study of etanercept in participants with systemic JIA, RF-positive or RF-negative polyarthritis, or eoJIA [25]. An analysis of data from the German BiKeR registry that included >2700 participants representing all categories of JIA who received etanercept over a period of 18 years did not report any new safety signals, particularly regarding risk of malignancy or autoimmune disorders other than IBD, which includes Crohn's disease [26]. Frequency of IBD was 0.3 per 100 patient-years (*vs* 0.03 EP100PY in the biologic-naïve group) and of the 19 participants affected, six were diagnosed with eoJIA and four with ERA. Clinical benefits of etanercept were maintained through up to 9 years of continuous treatment in that study. In a small registry-based observational study that included 20 etanercept-treated participants with ERA, declines in disease activity were observed within as few as 3 months of treatment and maintained through 15 months, with a favourable safety profile; however, inactive disease was not maintained among the few participants who had follow-up ≥27 months [27]. In a Dutch registry study that included 146 consecutive participants with any category of JIA, etanercept was associated with sustained responses up to 75 months, with few AEs and a low rate of SAEs [28].

Strengths of CLIPPER2 include the study duration, providing efficacy and safety assessments during up to 10 years of continuous treatment. Study limitations include the non-randomized, open-label design and lack of a control group. In addition, many participants had missing data or discontinued treatment during the 10-year study. The low participant numbers at later time points suggest that results should be interpreted with caution. Further, some secondary efficacy endpoints were introduced as a protocol amendment and not fully implemented until ∼12 months after the first-patient-first-visit. As a result, there were fewer efficacy data collected at Months 6 and 12 of CLIPPER compared with later time points. Finally, the withdrawal and re-treatment analyses are limited by the very small number of participants.

Conclusions

The safety profile of etanercept during the 10 years of total follow-up was similar to that in previous JIA studies and consistent with the known safety profile of etanercept. Efficacy results were consistent with the profile of etanercept. Responses were considered durable with continued long-term treatment in the participants still on active treatment. Overall, etanercept was well tolerated, and the benefit–risk assessment remains favourable in this population.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

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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