BJD
British Journal of Dermatology

Sustained long-term efficacy and safety of adalimumab in paediatric patients with severe chronic plaque psoriasis from a randomized, double-blind, phase III study

D. Thaçi,[1] K. Papp,[2] D. Marcoux,[3] L. Weibel,[4] A. Pinter,[5] P.-D. Ghislain,[6] I. Landells,[7] P.H. Hoeger,[8] K. Unnebrink,[9] M.M.B. Seyger,[10] D.A. Williams,[11] S. Rubant[9] and S. Philipp[12]

[1]Institute and Comprehensive Center for Inflammation Medicine, University of Lübeck, Ratzeburger Allee 160, 23435 Lübeck, Germany
[2]K Papp Clinical Research and Probity Medical Research, University of Western Ontario, Waterloo, ON, Canada
[3]CHU Sainte-Justine Montreal, Montreal, QC, Canada
[4]Pediatric Dermatology Department, University Children's Hospital Zurich, and Dermatology Department, University Hospital Zurich, Zurich, Switzerland
[5]University Clinic of Frankfurt am Main, Department of Dermatology, Venereology and Allergology, Frankfurt am Main, Germany
[6]UCL St Luc, Brussels, Belgium
[7]Nexus Clinical Research and Memorial University of Newfoundland, St John's, NL, Canada
[8]Department of Pediatric Dermatology, Catholic Children's Hospital, Hamburg, Germany
[9]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany
[10]Department of Dermatology and Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands
[11]AbbVie Inc., North Chicago, IL, U.S.A.
[12]Department of Dermatology, Venerology and Allergy, Charité Universitätsmedizin Berlin, Berlin, Germany

Linked Comment: Belloni Fortina and Caroppo. Br J Dermatol 2019; **181**:1127–1128.

Correspondence
Diamant Thaçi.
E-mail: Diamant.Thaci@uksh.de

Accepted for publication
22 April 2019

Funding sources
Funding sources can be found in the Appendix.

Conflicts of interest
Conflict of interest statements can be found in the Appendix.

DOI 10.1111/bjd.18029

Summary

Background Adalimumab (ADA) (Humira®, AbbVie Inc., U.S.A.) is approved by the European Medicines Agency for children aged ≥ 4 years with severe plaque psoriasis.
Objectives To evaluate the long-term efficacy and safety of ADA in children with severe plaque psoriasis.
Methods Results are presented from the 52-week long-term extension (LTE) of the randomized, double-blind, double-dummy, phase III trial, in children with severe plaque psoriasis (results from prior periods have been published). Patients aged ≥ 4 and < 18 years were randomized 1 : 1 : 1 to ADA 0·8 mg kg^{-1} (40 mg maximum) or 0·4 mg kg^{-1} (20 mg maximum) every other week or to methotrexate (MTX) 0·1–0·4 mg kg^{-1} (25 mg maximum) weekly. The 16-week initial treatment (IT) period was followed by a 36-week withdrawal period and a 16-week retreatment period. Patients could enter the LTE at prespecified time points to receive ADA 0·8 mg kg^{-1} (blinded or open label) or ADA 0·4 mg kg^{-1} (blinded), or to remain off treatment. Efficacy is reported for patient groups according to doses received in the IT and LTE periods.
Results Of the 114 patients randomized in the IT period, 108 entered the LTE (n = 36 in each group); 93 received ADA 0·8 mg kg^{-1}. Efficacy (≥ 75% improvement from baseline in Psoriasis Area and Severity Index) was maintained or improved from entry to the end of the LTE: MTX(IT)/ADA 0·8(LTE) 31–86% of patients; ADA 0·4(IT)/0·4 or 0·8(LTE) 28–47%; ADA 0·8(IT)/0·8(LTE) 50–72%. No serious infections occurred in the LTE.
Conclusions After 52 weeks of long-term ADA treatment in children aged 4–18 years with severe plaque psoriasis, disease severity was reduced and maintained or further improved, as demonstrated by efficacy outcomes. No new safety risks were identified.

What's already known about this topic?

- The results from the first three periods of this phase III trial in children aged 4–18 years with severe plaque psoriasis suggest that adalimumab is a safe and efficacious treatment option in this population.

What does this study add?

- This is the first study to evaluate long-term treatment of adalimumab in children with severe psoriasis, and the first to evaluate switching from methotrexate to adalimumab in this population.

Plaque psoriasis is a chronic inflammatory skin disease. Its overall prevalence for children 0–18 years of age is 0·2–1·4% in Europe and approximately 1% in the U.S.A.[1,2] The disease in children and adults is associated with impaired quality of life[3–5] and an increased risk of comorbidities, including obesity, metabolic syndrome, cardiovascular risk, autoimmune diseases[6–8] and psychosocial issues, especially depression.[9–11]

The limited number of approved systemic therapies and randomized controlled trials evaluating treatment in children has challenged the effective management of the disease. Conventional treatment options include topical therapy for mild-to-moderate disease,[12] and for severe or refractory disease, ultraviolet (UV)B phototherapy, narrowband UVB therapy if accessible and systemic treatments, including methotrexate (MTX), ciclosporin, acitretin (retinoids) and biologics.[13–15]

Approved biologic therapies for plaque psoriasis in children include the tumour necrosis factor (TNF)-α inhibitors etanercept[16–19] and adalimumab (ADA),[20] and the p40 inhibitor ustekinumab.[18,19] Etanercept is approved by the European Medicines Agency (EMA) for children aged ≥ 6 years with severe disease, and by the U.S. Food and Drug Administration (FDA) for children aged ≥ 4 years; ADA is approved by the EMA for children aged ≥ 4 years with severe chronic disease; and ustekinumab is approved by the EMA and FDA for children aged ≥ 12 years with moderate-to-severe disease.

Results of long-term treatment of children with moderate-to-severe psoriasis have been published for open-label etanercept,[21,22] and for ustekinumab vs. placebo.[23] Biologic treatment of psoriasis in children is reported as less likely to result in adverse events or in treatment discontinuation compared with MTX.[24]

The current analysis reports results from the first randomized 52-week controlled trial, comparing the efficacy and safety of a biologic treatment, ADA (Humira®, AbbVie Inc., North Chicago, IL, U.S.A.), a recombinant fully human monoclonal antibody directed against TNF-α, with the active comparator MTX, in children with severe plaque psoriasis. Results from the first three periods of this trial have been reported.[25]

Patients and methods

Participants

Patients were children aged ≥ 4 and < 18 years with a body weight of ≥ 15 kg and severe plaque psoriasis for ≥ 6 months, who had failed to respond to topical therapy. Severe psoriasis was defined as meeting at least one of the following criteria: (i) Physician's Global Assessment (PGA) ≥ 4; (ii) body surface area involved > 20%, or > 10% with very thick lesions; (iii) Psoriasis Area and Severity Index (PASI) > 20, or PASI > 10 and at least one of the following: active psoriatic arthritis unresponsive to nonsteroidal anti-inflammatory drugs, Children's Dermatology Life Quality Index (CDLQI) >10, or clinically relevant facial, genital or hand and/or foot involvement. Prior use of biologics was not allowed, with the exception of etanercept (treatment up to 4 weeks before the baseline visit was allowed). Allowed concomitant medications during the study included medicated (noncorticosteroid) shampoos, bland (without beta- or alpha-hydroxy acids) emollients, and inhaled corticosteroids for stable medical conditions. Additional study inclusion criteria have been published.[25]

Study design

This randomized, parallel-group, double-blind, phase III study (ClinicalTrials.gov: NCT01251614) had four periods: primary double-blind initial treatment (IT, 16 weeks), withdrawal (up to 36 weeks), retreatment (16 weeks) and long-term extension (LTE, 52 weeks) (Fig. 1). Results from the LTE are presented here.

Patients received blinded ADA 0·8 mg kg^{-1} (up to 40 mg total dose) or ADA 0·4 mg kg^{-1} (up to 20 mg total dose) at week 0 and then every other week starting at week 1, or 0·1–0·4 mg kg^{-1} MTX weekly (up to 25 mg per week total dose; uptitrated for efficacy, as tolerated). Responders and nonresponders were defined based on achievement of the primary end points at week 16: ≥ 75% improvement from baseline in PASI (PASI 75) and PGA of cleared (0) or minimal (1) disease (PGA 0/1). The LTE was conducted in parallel to the other study periods for up to 52 weeks and could be entered at multiple time points (Fig. 1).

Evaluations

In the LTE, efficacy was summarized for three patient groups, defined according to their initial randomized dose in the IT period and the dose received in the LTE: MTX (IT)/ADA 0·8 (LTE); ADA 0·4 (IT)/0·4 or 0·8 (LTE); and ADA 0·8 (IT)/0·8 (LTE). Given the study design, LTE dosing was complex; the majority of patients received ADA 0·8 mg kg^{-1} (open label or blinded) at the start of or during the LTE, and as continued treatment from the retreatment period or after switching from treatment withdrawal or from ADA 0·4 mg kg^{-1} during the LTE. For this reason, we report results for all patients who entered the LTE, despite how, when or whether they received ADA 0·8 mg kg^{-1}.

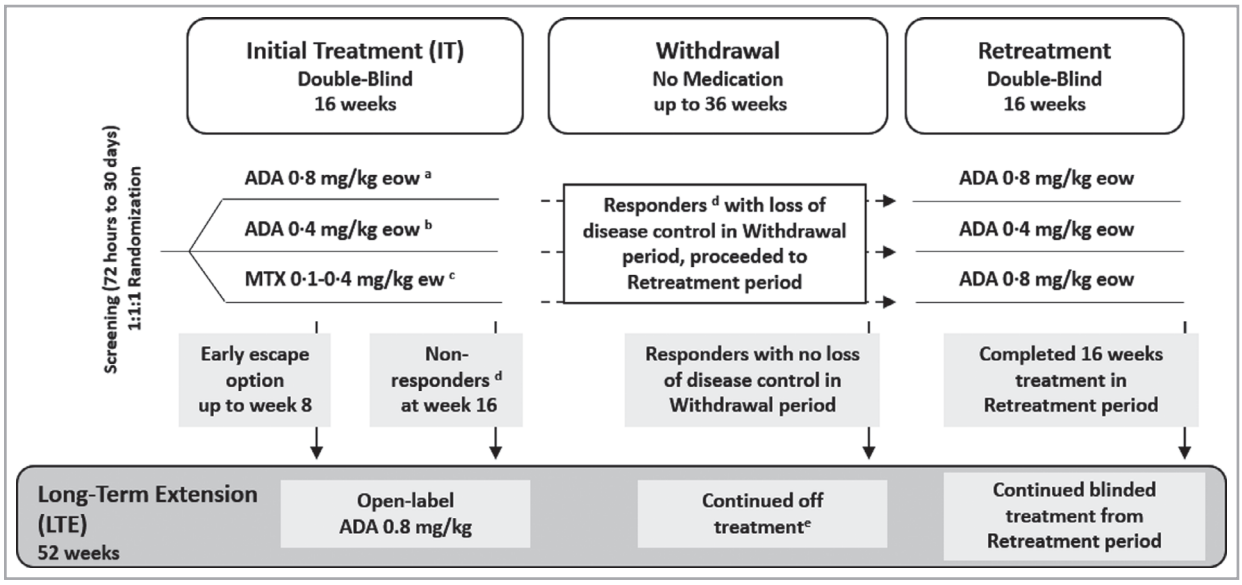

Fig 1. Study design. [a]Adalimumab (ADA) 0·8 mg kg^{-1} up to 40 mg at week 0; every other week (eow) from week 1. [b]ADA 0·4 mg kg^{-1} up to 20 mg at week 0; eow from week 1. [c]Methotrexate (MTX) 0·1–0·4 mg kg^{-1} every week (ew) up to 25 mg per week. [d]Responders or nonresponders were patients who achieved or did not achieve ≥ 75% improvement in Psoriasis Area and Severity Index and a Physician's Global Assessment (PGA) score of 0 or 1 at the end of the initial treatment (IT) period. [e]Patients who lost disease control in the long-term extension (LTE) could receive ADA until the end of the LTE at the initial randomized dose, or ADA 0·8 mg kg^{-1} if the initial randomized drug was MTX. Patients entering the withdrawal period initially randomized to MTX received blinded ADA 0·8 mg kg^{-1} in the retreatment period and the LTE. Patients initially randomized to ADA 0·4 mg kg^{-1} or 0·8 mg kg^{-1} received blinded ADA in the retreatment period and the LTE based on their initial randomized dose. All patients had a dose-increase option to open-label ADA 0·8 mg kg^{-1} in the LTE.

Other LTE evaluations included the CDLQI and the Pediatric Quality of Life Inventory. Absolute PASI values at score categories ≤ 5 and ≤ 3 were analysed post hoc across the IT period and the LTE. Safety was evaluated by treatment-emergent adverse events. Efficacy and safety were also evaluated for the subgroup of patients who failed MTX treatment in the IT period and were switched to ADA 0·8 mg kg^{-1} in the LTE.

Statistical analysis

Efficacy was evaluated for all randomized patients (intention-to-treat population) in the IT period (n = 114); the statistical analysis and results have been reported previously.[25] In the LTE, the intention-to-treat population included all patients who entered the LTE (n = 108). Missing data were imputed using nonresponder imputation for dichotomous efficacy end points and last observation carried forward for continuous end points. The safety population consisted of all who received at least one dose of study medication in the trial. As the majority (92·6%, 100 of 108) of patients received ADA during the LTE, no statistical comparisons among efficacy groups were performed in the LTE.

Results

Of the 114 initially randomized patients (MTX, n = 37; ADA 0·4 mg kg^{-1}, n = 39; ADA 0·8 mg kg^{-1}, n = 38), 108 entered the LTE (n = 36 in each efficacy group) (Fig. 2). Patients who entered the LTE according to prespecified entry criteria included eight who escaped the IT period early (n = 6 at week 4 and n = 2 at week 8), 51 who were nonresponders at the end of the IT period, 15 who completed the IT period and did not lose disease control at the end of the treatment withdrawal period, and 34 who completed the IT period, lost disease control in the withdrawal period and completed the retreatment period.

The majority of the 108 patients who entered the LTE received ADA 0·8 mg kg^{-1} in the LTE (Fig. 2): 100 received any ADA (0·4 or 0·8 mg kg^{-1}) and 93 received any ADA 0·8 mg kg^{-1} dose. Of these, 83 of 93 received open-label or blinded ADA 0·8 mg kg^{-1} from the start of the LTE, and 88 of 93 received ADA 0·8 mg kg^{-1} from their first dose in the LTE. Four of 93 patients started the LTE off drug, lost disease control and were switched to blinded ADA 0·8 mg kg^{-1} in the LTE, and an additional six of 93 switched from double-blind ADA 0·4 mg kg^{-1} to open-label ADA 0·8 mg kg^{-1} in the LTE (Fig. 2).

Eight of the 15 patients who did not lose disease control in the withdrawal period and who continued off treatment in the LTE remained off drug in the LTE, and seven of 15 lost disease control in the LTE and were re-treated with the same blinded dose they received in the IT period (or with ADA 0·8 mg kg^{-1} for those initially randomized to MTX in the IT period); this included three who were re-treated in the LTE with ADA 0·4 mg kg^{-1} and four who were re-treated with ADA 0·8 mg kg^{-1}.

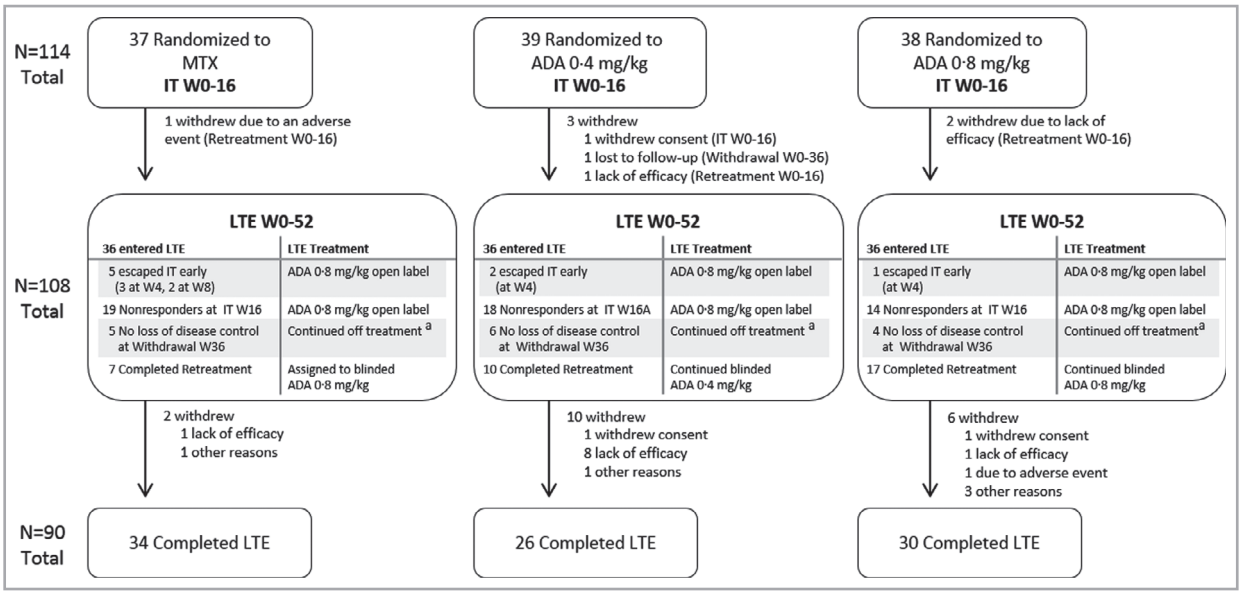

Fig 2. Patient disposition. Efficacy in the long-term extension (LTE) was analysed for three groups, defined by the initial randomized dose (initial treatment, IT) and the dose received in the LTE. [a]Patients entering the LTE from the withdrawal period with no loss of disease control who subsequently lost response in the LTE could be re-treated with blinded adalimumab (ADA) [at the same initial randomized dose or ADA 0·8 mg kg^{-1} if initially randomized to methotrexate (MTX)]. Of the 15 patients who did not lose disease control in the withdrawal period and continued off treatment in the LTE, eight remained off drug in the LTE [three MTX(IT)/ADA 0·8(LTE), three ADA 0·4(IT)/0·4 or 0·8(LTE), two ADA 0·8 (IT)/0·8(LTE)] and seven lost disease control in the LTE and were re-treated with the same dose they received in the IT period or with ADA 0·8 mg kg^{-1} if initially randomized to MTX [two MTX(IT) and two ADA 0·8(IT) were re-treated with ADA 0·8 mg kg^{-1} in the LTE, and three ADA 0·4(IT) were re-treated with ADA 0·4 mg kg^{-1} in the LTE]. Of the patients initially treated with ADA 0·4 mg kg^{-1} who entered the LTE, six switched to ADA 0·8 mg kg^{-1} open label during the LTE. W, week.

In total 18 of 108 patients (16·7%) discontinued the LTE; the primary reason was lack of efficacy (n = 10). The median exposure to any ADA dose was 364 days (range 42–380) during the LTE (n = 100), and 392 days (range 21–611) during the entire study (n = 111). The baseline demographics and disease characteristics were balanced among the IT-period dose groups.[25] The most commonly reported concomitant topical medications were salicylic acid (6%) and emollients and protectives (5·3%).

At baseline, the mean ± SD patient body weight (51·3 ± 20·3 kg) and body mass index (BMI) (21·1 ± 4·9 kg m^{-2}) were balanced across baseline treatment groups (MTX, ADA 0·4 mg, ADA 0·8 mg). The numbers of patients in each BMI category (based on age- and sex-specific World Health Organization BMI charts) were 68 of 114 (59·6%) normal weight, 17 (14·9%) overweight and 24 (21·1%) obese; the percentages of patients within each category were also balanced across baseline treatment groups.[25]

There were no trends regarding the percentages of patients achieving PASI 75 across the BMI categories of normal weight, overweight and obese: MTX(IT)/ADA 0·8(LTE), 90%, 100%, 63% (n = 21, 6, 8, respectively); ADA 0·4(IT)/ADA 0·4 or 0·8(LTE), 48%, 50%, 50% (n = 23, 4, 8, respectively); ADA 0·8(IT)/ADA 0·8(LTE), 75%, 57%, 83% (n = 20, 7, 6, respectively). The small numbers of patients in each of the overweight and obese categories limit any interpretation of these results.

Efficacy

Treatment response, measured by achievement of PASI 75, PASI 90 and PASI 100, improved for all efficacy groups from the start of the LTE across 52 weeks of treatment (Fig. 3). At LTE week 52, PASI 75, 90 and 100 response rates for each efficacy group were higher than the corresponding rates at week 16 of the IT period. Response measured by achievement of PGA 0/1 also improved for all efficacy groups from the start of the LTE across 52 weeks of treatment, and rates at LTE week 52 for the MTX(IT)/ADA 0·8(LTE) and ADA 0·4(IT)/0·4 or 0·8(LTE) groups were higher than the corresponding rates at week 16 of the IT period (Fig. 4). Patients in the MTX(IT)/ADA 0·8(LTE) group had a higher response rate at LTE week 52 than those in the other two efficacy groups for all efficacy measures (Figs. 3 and 4).

Treatment response measured by absolute PASI ≤ 3 and ≤ 5 also improved for all three efficacy groups from the start of the LTE across 52 weeks of treatment, and the rates at week 52 for each efficacy group were higher than the corresponding rates at week 16 of the IT period, except for PASI ≤ 5 for the ADA 0·4(IT)/0·4 or 0·8(LTE) groups (Fig. 5).

Patients unresponsive to MTX in the IT period who at the end of that period were transitioned directly to the LTE to receive open-label ADA 0·8 mg kg^{-1} experienced improved treatment response as measured by PASI 75 and PASI 90 as early as 4 weeks after switching to ADA, and generally

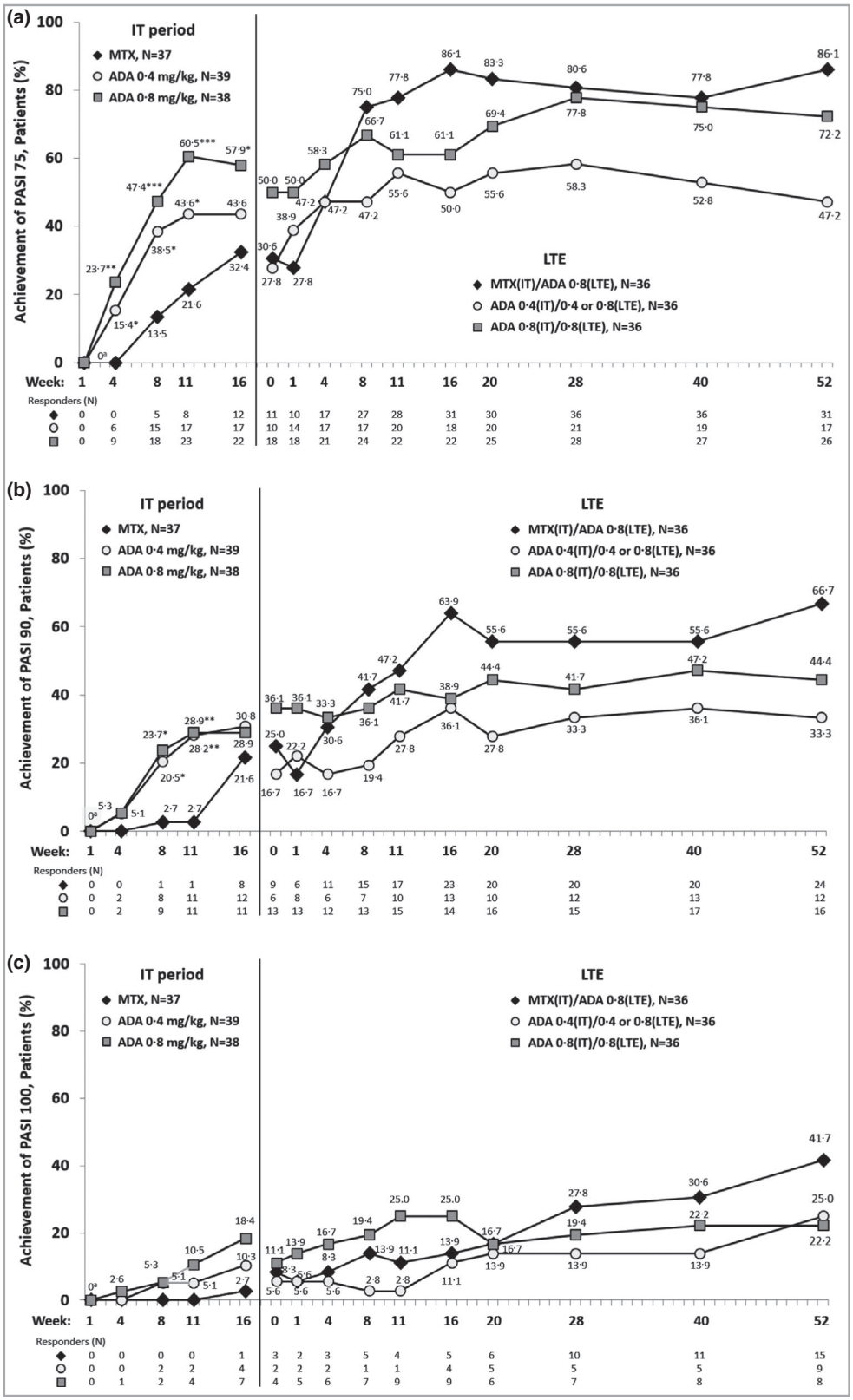

Fig 3. Proportions of patients achieving (a) ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75), (b) PASI 90 and (c) PASI 100 response (intention-to-treat population; nonresponder imputation). [a]0% for PASI 75, 90 and 100 at initial treatment (IT) week 1 for all dose groups and at IT week 4 for methotrexate (MTX); 0% for PASI 100 at IT week 4 for adalimumab (ADA) 0·4 mg kg^{-1}, and at IT weeks 8 and 11 for MTX. Statistically significant at ***P = 0·001, **P = 0·01, *P = 0·05 levels for MTX vs. ADA 0·4 mg kg^{-1} or MTX vs. ADA 0·8 mg kg^{-1} dosage in the IT period. Efficacy groups in the long-term extension (LTE) are defined based on the initial randomization assignment in the IT period and on the dose received in the LTE.

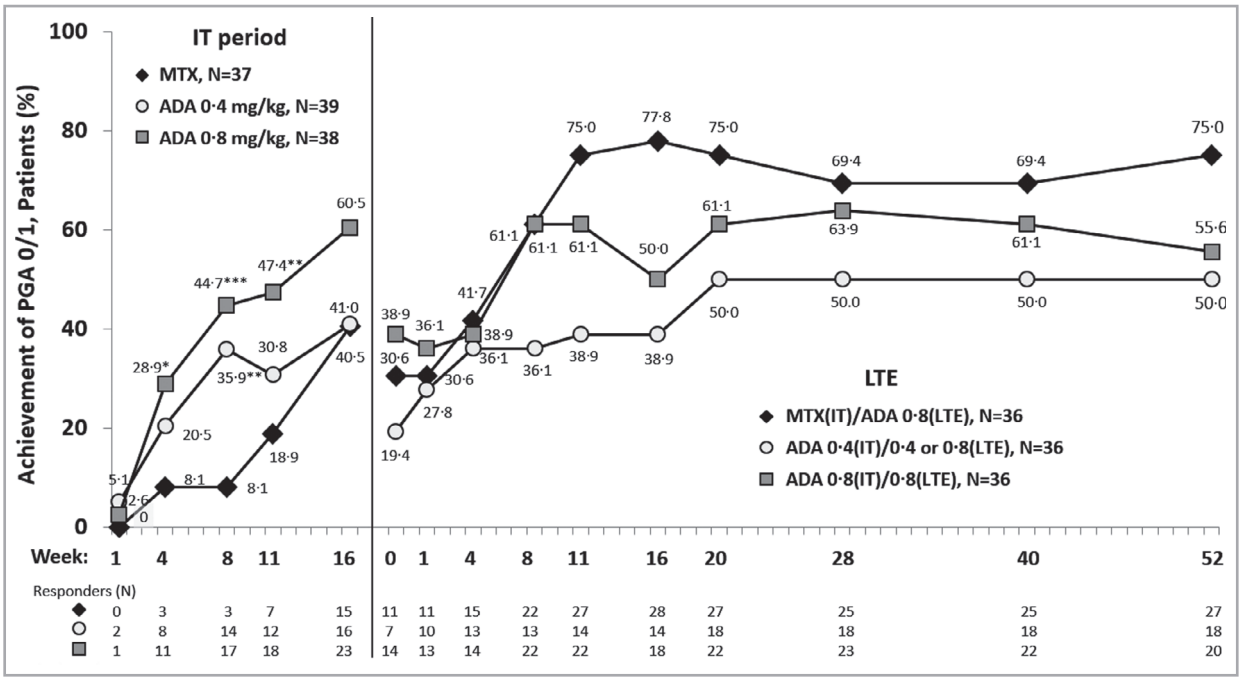

Fig 4. Achievement of Physician's Global Assessment (PGA) 0 or 1 response (intention-to-treat population; nonresponder imputation). Statistically significant at ***$P = 0{\cdot}001$, **$P = 0{\cdot}01$, *$P = 0{\cdot}05$ levels for methotrexate (MTX) vs. adalimumab (ADA) 0·4 mg kg^{-1} or MTX vs. ADA 0·8 mg kg^{-1} dosage in the initial treatment (IT) period. Efficacy groups in the long-term extension (LTE) are defined based on the initial randomization assignment in the IT period, and on the dose received in the LTE.

maintained the respective level of response through the rest of the LTE (Fig. 6a). The PASI 100 response rate for these patients also improved starting at LTE week 4, and continued to improve to the end of the period (Fig. 6a). The PGA 0/1 response rate improved from weeks 1 to 11 and then slightly decreased by the end of the period (Fig. 6b).

Improvements in quality-of-life scores during the LTE were highest for patients initially randomized to ADA 0·8 mg kg^{-1}. For all efficacy groups, quality-of-life scores at the end of the IT period, as measured by CDLQI and Pediatric Quality of Life Inventory, improved across the 52 weeks of the LTE (Table 1).

Safety

During the LTE, there were 407·4 adverse events per 100 patient-years (PYs) (Table 2). The most frequently reported events (≥ 20% of patients) were nasopharyngitis and headache. Injection-site reactions occurred in 3·7% of patients (four of 108). There were no malignancies.

Five serious adverse events occurred during the LTE (five of 108, 4·6% overall) (Table 2). Eight patients (eight of 108, 7·4%) reported severe adverse events, one of whom discontinued the study drug (Table 2). One patient had a moderate event of herpes zoster in the LTE that the investigator considered to be possibly related to ADA. Overall, a higher rate of events related to allergic reactions (urticaria, pruritus, bronchospasm and asthma) was seen for patients initially randomized to MTX (18·2 events per 100 PYs) than for patients initially randomized to ADA (4·5 events per 100 PYs); there were no serious events related to allergic reaction.

For patients who failed MTX at week 16 of the IT period (n = 19), the rate of adverse events during the LTE was 381·5 per 100 PYs for any event, 5·7 per 100 PYs for serious events, 142·2 per 100 PYs for infections and 56·9 per 100 PYs for events at least possibly related to ADA.

There were no serious infections. Infections included upper respiratory tract infection (n = 5), nasopharyngitis (n = 4), rhinitis (n = 2), influenza (n = 2), pharyngitis (n = 2), bronchitis (n = 2), oral herpes (n = 1), gastroenteritis (n = 1), otitis media (n = 1) and urinary tract infection (n = 1).

Discussion

Treatment of children with severe chronic psoriasis remains a challenge. Standardized treatment guidelines are lacking and the evidence for the efficacy and safety of systemic treatments in paediatric psoriasis is limited. The treatment approach is based on systemic treatments for adults, even though most of these drugs are not approved for paediatric use.[26] While MTX was first investigated in this clinical trial, only retrospective case series are available for drugs such as ciclosporin and acitretin.[26–28] The chronicity of psoriasis and its negative effect on patient quality of life can necessitate long-term treatment, thus the efficacy and safety of long-term systemic therapy are important in this population. However, they have been evaluated in only a few clinical trials, which show the strongest evidence for

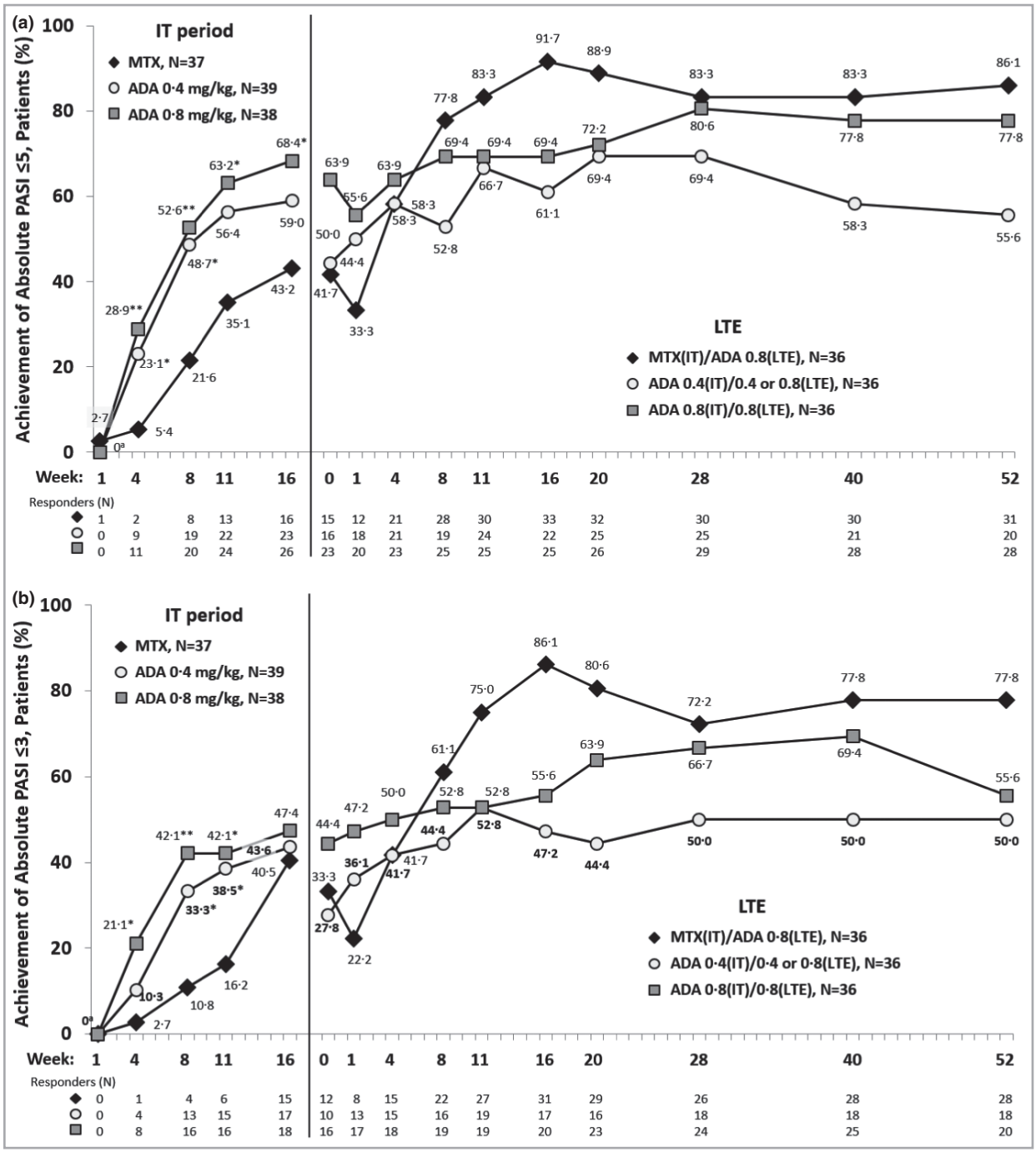

Fig 5. Achievement of absolute Psoriasis Area and Severity Index (PASI) ≤ 5 and ≤ 3 (intention-to-treat population; nonresponder imputation). (a) Absolute PASI ≤ 5. (b) Absolute PASI ≤ 3. Statistically significant at **P = 0·01, *P = 0·05 levels for methotrexate (MTX) vs. adalimumab (ADA) 0·4 mg kg^{-1} or MTX vs. ADA 0·8 mg kg^{-1} dosage in the initial treatment (IT) period. Efficacy groups in the long-term extension (LTE) are defined based on the initial randomization assignment in the IT period, and on the dose received in the LTE.

biologics.[21–23,29] Methotrexate is approved for adult plaque psoriasis only, but up to now has been the first-line systemic agent recommended for paediatric psoriasis.[14]

Biologics have significantly changed psoriasis treatment over the decades and have greatly improved patients' health-related quality of life and patient-relevant outcomes.[30–33] ADA has been used to treat adults with moderate-to-severe plaque psoriasis for over a decade, and has shown superior efficacy to systemic treatments, such as MTX. Its accumulating safety data resulted in a first-line label for adults and children.[34,35] By blocking TNF-α, ADA inhibits inflammation in psoriatic lesions by decreasing the level of proinflammatory cytokines. Other

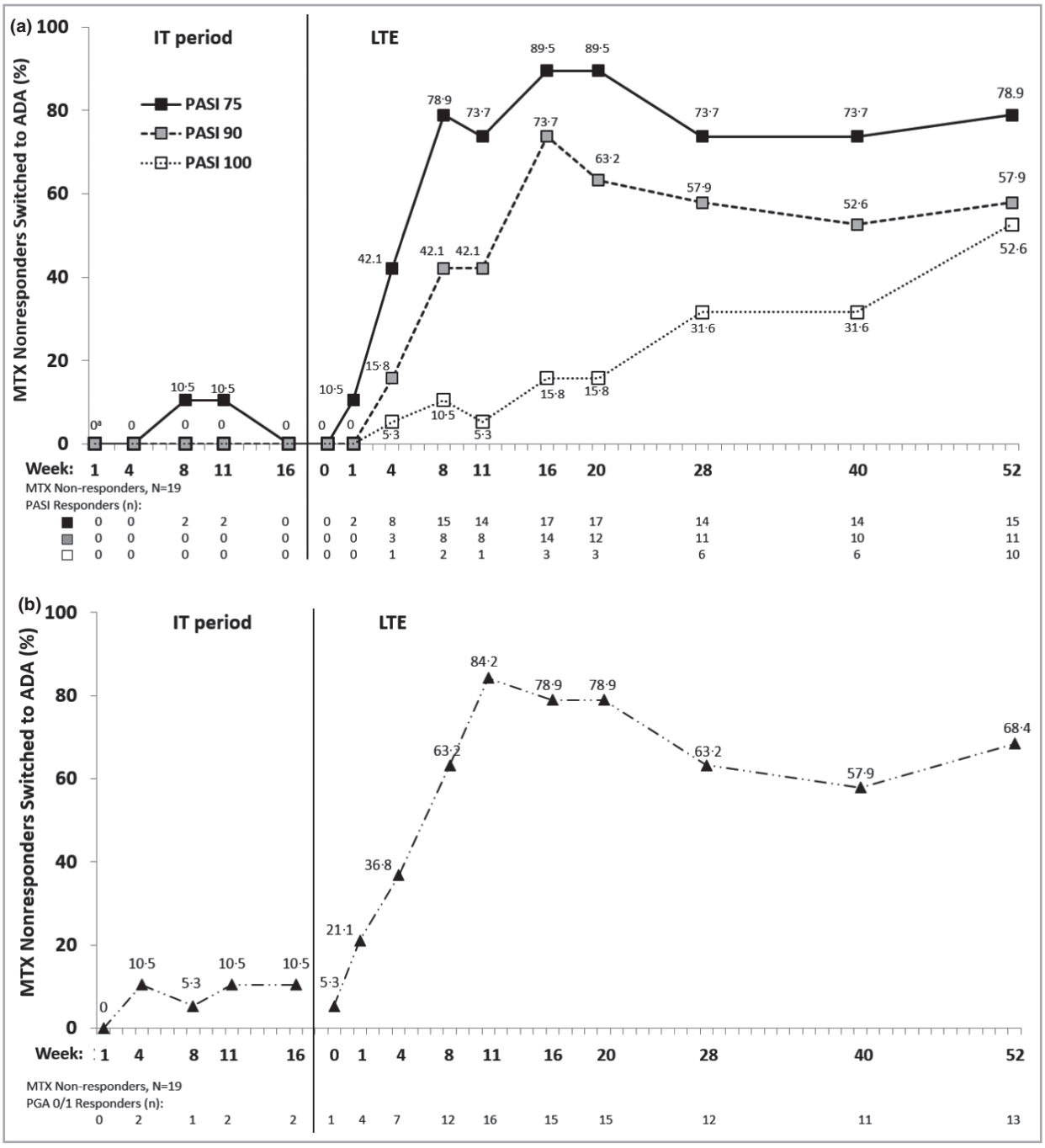

Fig 6. Efficacy for methotrexate (MTX) nonresponders at week 16 who switched to adalimumab (ADA) in the long-term extension (LTE) (intention-to-treat population; nonresponder imputation). (a) ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75), PASI 90 and PASI 100. (b) Physician's Global Assessment (PGA) score of 0 or 1. There were 19 patients who failed MTX treatment in the initial treatment (IT) period, entered the long-term extension (LTE) at the end of the IT period (week 16) and received open-label ADA 0·8 mg kg^{-1} during the LTE.

biologics approved for the treatment of children with plaque psoriasis are etanercept (age ≥ 6 years with severe disease) and ustekinumab (age ≥ 12 years with moderate-to-severe disease).

In this active-comparator-controlled study, response at the end of the initial 16 weeks to ADA 0·8 mg kg^{-1} was maintained through the 52-week LTE period of this trial. These results in children with severe psoriasis are consistent with results from ADA clinical trials in adults with moderate-to-severe psoriasis. In an analysis of 250 adults, PASI 75, 90 and 100 rates after 160 weeks of ADA treatment were 76%, 50% and 31%, respectively,[36] compared with 68·5%, 48·1% and 29·6% of children overall in the current study. In an interim analysis from a 10-year observational registry of ADA treatment in adults (n = 6059), PGA 0/1 was achieved

Table 1 Quality-of-life outcomes (intention-to-treat population, last observation carried forward)

		Efficacy groups (by treatment received in the IT and LTE periods)		
Quality-of-life measure	Week/period	MTX(IT)/ADA 0·8(LTE)	ADA 0·4(IT)/0·4 or 0·8(LTE)	ADA 0·8(IT)/0·8(LTE)
CDLQI[a]		n = 36, week 16/IT n = 35, week 52/LTE	n = 37, week 16/IT n = 34, week 52/LTE	n = 38, week 16/IT n = 36, week 52/LTE
% change from BL, mean ± SD	16/IT	−40·0 ± 58·4	−45·8 ± 55·2	−57·2 ± 48·3
	52/LTE	−70·0 ± 53·5	−55·0 ± 46·7	−67·2 ± 43·2
% change from BL, median (IQR)	16/IT	−64·8 (−82·4, −13·8)	−62·5 (−90·0, 0)	−73·6 (−94·4, −40·9)
	52/LTE	−93·3 (−100·0, −60·0)	−74·2 (−90·9, −27·3)	−86·9 (−100·0, −50·0)
PedsQL[b]		n = 37, week 16/IT n = 36, week 52/LTE	n = 38, week 16/IT n = 36, week 52/LTE	n = 38, week 16/IT n = 36, week 52/LTE
% change from BL, mean ± SD	16/IT	3·0 ± 14·7	18·5 ± 28·2	18·6 ± 30·2
	52/LTE	14·3 ± 28·8	61·0 ± 219·5	24·3 ± 32·7
% change from BL, median (IQR)	16/IT	4·5 (−4·8, 10·0)	10·4 (3·2, 22·9)	10·5 (0, 29·3)
	52/LTE	9·6 (3·0, 18·1)	17·0 (4·0, 30·2)	13·0 (3·7, 30·3)

ADA, adalimumab; BL, baseline; CDLQI, Children's Dermatology Life Quality Index; IT, initial treatment; LTE, long-term extension; MTX, methotrexate; PedsQL, Pediatric Quality of Life Inventory. [a]Negative change indicates improvement. [b]Positive change indicates improvement.

between 3 and 5 years of treatment by > 60% of adults, compared with 60·2% of children overall in the current study.[37]

Similar results have also been reported in trials of other biologic therapies approved for moderate-to-severe psoriasis in children. A 5-year open-label extension study of etanercept confirmed its efficacy (70%, 40% and 50% achievement rates for PASI 75, PASI 90 and PGA 0/1) following long-term treatment, with no new safety concerns.[21] In a 52-week randomized, placebo-controlled trial, response rates for the standard ustekinumab dose were generally maintained from week 12 through 1 year (PASI 75, 80·6%; PASI 90, 61·1%; PGA 0/1, 69·4%), with no unexpected adverse events.[23]

Using absolute PASI as a treatment goal may provide more objective clinical information about the efficacy of a treatment, as it reflects the improvement of a patient's disease severity independently from the baseline value. The achievement rate of each absolute PASI cut-off (≤ 5 and ≤ 3) in this study was numerically higher at week 52 of the LTE than at LTE entry, for each LTE efficacy group, and thus may represent a treatment goal achievement of minor disease symptoms.

Patients with psoriasis onset at a young age are likely to have more depression, sleep problems and social discrimination, and a higher lifetime Dermatology Life Quality Index,[38,39] even more so with severe psoriasis. Physical, psychological and social impairments might have a significant impact on the development of these patients and might result in an inability to achieve 'full-life potential' (also termed cumulative life course impairment) early in their lives.[40] Therefore, there is still an unmet medical need to provide long-term effective and safe psoriasis therapy to patients at a young age in order to control disease chronicity and limit its consequences on patient quality of life. The results from this first comparative study showed that at the initial 16 weeks, patients' quality of life improved in relation to their clinical response, and was maintained throughout the 52-week period. Patients initially randomized to ADA 0·8 mg kg^{-1} showed the greatest mean improvement in quality-of-life scores during the LTE compared with the other groups.

For the subgroup who did not respond to MTX treatment in the IT period and continued directly to open-label treatment with ADA 0·8 mg kg^{-1} in the LTE, the majority achieved PASI 75, PASI 90 and PGA 0/1 (80%) response throughout the LTE, starting as early as week 4. This improvement after switching is consistent with results of other trials in adults with moderate-to-severe psoriasis. In an open-label trial, 61% of patients (n = 41) who had failed prior treatment with MTX achieved PGA 0/1 after 16 weeks of ADA.[41] In an open-label randomized controlled trial, patients who switched from initial treatment with MTX (n = 215) to infliximab (n = 63) had a higher response rate at week 26 than patients who did not switch (73% vs. 30·7% achieved PASI 75, and 75% vs. 28% achieved PGA 0/1).[42] In a real-world practice study, patients (n = 267) improved their skin response following a switch to biologics after treatment with conventional systemic agents. In that study the mean time to first follow-up after switching was 6 weeks, and the mean ± SD PASI scores before and after switching were 13·6 ± 8·8 and 5·7 ± 5·8, respectively.[43]

In the current study, following ADA 0·8 mg kg^{-1} treatment in the LTE, the MTX responders in the IT period had a generally greater treatment response rate across efficacy outcomes than MTX nonresponders in the IT period. Possible reasons include lack of a washout period for nonresponders, or more patients who escaped early in the IT period entering the LTE. In general, the response rates for both groups were greater than the rates in the LTE for patients who received ADA in the IT period and in the LTE.

The ADA safety profile across all efficacy groups during the 52-week LTE was similar to the 16-week IT period profile,[25] including low numbers of serious adverse events, severe adverse events, injection-site reactions and allergic reactions, and was therefore consistent with the known safety profile of

Table 2 Treatment-emergent adverse events in the long-term extension (LTE)

	Efficacy group (by treatment received in the IT and LTE periods)			
	MTX(IT)/ADA 0·8(LTE), n =36 31·10 PYs	ADA 0·4(IT)/0·4 or 0·8(LTE), n =36 24·81 PYs	ADA 0·8(IT)/ 0·8(LTE), n =36 30·73 PYs	Total, n =108[a] 86·64 PYs
AEs, n (per 100 PYs)				
Any AE	144 (463·0)	90 (362·8)	199 (387·2)	353 (407·4)
Serious AE	1 (3·2)	1 (4·0)	3 (9·8)	5 (5·8)
Severe AE	4 (12·9)	3 (12·1)	2 (6·5)	9 (10·4)
AE leading to study discontinuation	0	1 (4·0)	1 (3·3)	2 (3·6)
Infections	41 (131·8)	37 (149·1)	47 (152·9)	125 (144·3)
Serious infections	0	0	0	0
Tuberculosis	0	1 (4·0)	1 (3·3)	2 (2·3)
Worsening/new onset of psoriasis	2 (6·4)	4 (16·1)	2 (6·5)	8 (9·2)
Allergic reaction[b]	4 (12·9)	0	0	4 (4·5)
Injection-site reaction	1 (3·2)	1 (4·0)	5 (16·3)	7 (8·1)
AE leading to death[c]	0	0	1 (3·3)	1 (1·2)
AEs, n (%)				
Any AE	28 (78)	24 (67)	33 (92)	85 (78·7)
Serious AE[d]	1 (3)	1 (3)	3 (8)	5 (4·6)
Severe AE[e]	3 (8)	3 (8)	2 (6)	8 (7·4)
AE leading to study discontinuation	0	1 (3)	1 (3)	2 (1·9)
Infections	22 (61)	15 (42)	25 (69)	62 (57·4)
Serious infections	0	0	0	0
Tuberculosis	0	1 (3)	1 (3)	2 (1·9)
Worsening/new onset of psoriasis	2 (6)	4 (11)	2 (6)	8 (7·4)
Allergic reaction[b]	3 (8)	0	0	3 (2·8)
Injection-site reaction	1 (3)	1 (3)	2 (6)	4 (3·7)
AE leading to death[c]	0	0	1 (3)	1 (0·9)
Most common AEs (≥ 10% of patients overall)				
Nasopharyngitis	7 (19)	7 (19)	14 (39)	28 (25·9)
Headache	5 (14)	6 (17)	12 (33)	23 (21·3)
Upper respiratory tract infection	7 (19)	2 (6)	4 (11)	13 (12·0)
Nausea	3 (8)	3 (8)	5 (14)	11 (10·2)

ADA, adalimumab; AE, adverse event; IT, initial treatment; MTX, methotrexate; PY, patient-years. [a]Included patients who received at least one dose of study drug during the trial. [b]Included angio-oedema, anaphylaxis, lupus-like reactions and systemic lupus erythematosus. [c]Accidental fall leading to death. [d]Serious events included death from accidental fall 11 days post-treatment [ADA 0·8(IT)/0·8(LTE), n = 1], chest pain [MTX(IT)/ADA 0·8(LTE), n = 1], tendon injury [ADA 0·4(IT)/0·4 or 0·8(LTE), n = 1], eye naevus [ADA 0·8(IT)/0·8(LTE, n = 1] and maculopapular rash [ADA 0·8(IT)/0·8(LTE), n = 1], all considered by the investigator as not or probably not related to the study drug, except eye naevus (possibly related). (e) Severe events included fall, chest pain and tendon injury (see 'd' above), as well as events in one patient each of abdominal pain, bronchitis and extremity pain [MTX(IT)/ADA 0·8(LTE)], upper respiratory tract infection [ADA 0·4(IT)/0·4 or 0·8(LTE), n = 1; ADA 0·8(IT)/0·8(LTE), n = 1] and psoriasis worsening [ADA 0·4(IT)/ADA 0·4 or 0·8(LTE), n = 1] resulting in ADA discontinuation. There were no infectious AEs of oral candidiasis or active tuberculosis, and no malignancies.

ADA in adults with psoriasis. No serious infections were observed during the LTE. Rates for adverse events leading to discontinuation, allergic reactions or injection-site reactions were low. The most common adverse events were nasopharyngitis and upper respiratory tract infections.

Similar safety results were seen in the long-term etanercept (n = 182) and ustekinumab (n = 110) trials in children with moderate-to-severe psoriasis,[21,23] including the rate of the more common adverse events of nasopharyngitis (25·9% ADA, 26·0% etanercept) and upper respiratory tract infection (12·0% ADA, 12·7% ustekinumab). Low rates were observed (ADA, etanercept and ustekinumab, respectively) for serious adverse events (4·6%, 3·8% and 4·5%), serious infections (0%, 1·1% and 1·8%), tuberculosis (1·9%, not reported and 0%) and injection-site reactions (3·7%, 8·8% and 0·9%). No malignancies or opportunistic infections were observed in any of these long-term trials.

The long-term safety profile of ADA from this study is also supported by the safety profiles from other trials of long-term ADA treatment of adults and children with psoriasis and other indications (rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis and Crohn disease). The adverse events observed in these trials and analyses are similar to those experienced by the current paediatric

population.[35–37,44,45] The rates of events per 100 PYs were similar across these trials and analyses. The adverse event rate for IT MTX responders who received ADA 0·8 mg kg^{-1} in the LTE was similar to the rates for patients receiving ADA in the other study periods.

A limitation of this study is the relatively small number of patients in each efficacy group during the LTE, which makes definitive conclusions difficult.

In conclusion, this study demonstrated that the efficacy of ADA 0·8 mg kg^{-1} dosed every other week was maintained through 52 weeks of treatment for this population of children with severe plaque psoriasis. For patients unresponsive to MTX after 16 weeks, treatment response improved after switching to open-label ADA 0·8 mg kg^{-1} every other week, and was generally maintained during 52 weeks of treatment in the extension period. No new safety risks were identified. These findings support the use of ADA as a long-term treatment option for children with severe plaque psoriasis.

Acknowledgments

The authors would like to acknowledge Monika Hoebel, employed by AbbVie, for statistical programming support. Editorial and medical writing support was provided by Jody Bennett, employed by AbbVie.

References

1 World Health Organization. Global Report on Psoriasis, 2016. Available at: http://www.who.int/iris/handle/10665/204417 (last accessed 3 June 2019).
2 Burden-Teh E, Thomas KS, Ratib S *et al.* The epidemiology of childhood psoriasis: a scoping review. *Br J Dermatol* 2016; **174**:1242–57.
3 Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br J Dermatol* 2006; **155**:145–51.
4 Gelfand JM, Feldman SR, Stern RS *et al.* Determinants of quality of life in patients with psoriasis: a study from the US population. *J Am Acad Dermatol* 2004; **51**:704–8.
5 Oostveen AM, de Jager ME, van de Kerkhof PC *et al.* The influence of treatments in daily clinical practice on the Children's Dermatology Life Quality Index in juvenile psoriasis: a longitudinal study from the Child-CAPTURE patient registry. *Br J Dermatol* 2012; **167**:145–9.
6 Volf EM, Levine DE, Michelon MA *et al.* Assessor-blinded study of the metabolic syndrome and surrogate markers of increased cardiovascular risk in children with moderate-to-severe psoriasis compared with age-matched population of children with warts. *J Drugs Dermatol* 2011; **10**:900–1.
7 Paller AS, Mercy K, Kwasny MJ *et al.* Association of pediatric psoriasis severity with excess and central adiposity: an international cross-sectional study. *JAMA Dermatol* 2013; **149**:166–76.
8 Augustin M, Radtke MA, Glaeske G *et al.* Epidemiology and comorbidity in children with psoriasis and atopic eczema. *Dermatology* 2015; **231**:35–40.
9 Gupta MA, Gupta AK. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. *Br J Dermatol* 1998; **139**:846–50.
10 Russo PA, Ilchef R, Cooper AJ. Psychiatric morbidity in psoriasis: a review. *Australas J Dermatol* 2004; **45**:155–9.
11 Matusiewicz D, Koerber A, Schadendorf D *et al.* Childhood psoriasis – an analysis of German health insurance data. *Pediatr Dermatol* 2014; **31**:8–13.
12 Silverberg NB. Pediatric psoriasis: an update. *Ther Clin Risk Manag* 2009; **5**:849–56.
13 Cordoro KM. Systemic and light therapies for the management of childhood psoriasis: part II. *Skin Ther Lett* 2008; **13**:1–3.
14 van Geel MJ, Mul K, de Jager ME *et al.* Systemic treatments in paediatric psoriasis: a systematic evidence-based update. *J Eur Acad Dermatol Venereol* 2015; **29**:425–37.
15 Marqueling AL, Cordoro KM. Systemic treatments for severe pediatric psoriasis: a practical approach. *Dermatol Clin* 2013; **31**:267–88.
16 Amgen. Enbrel (etanercept). Package insert. Available at: https://www.enbrel.com (last accessed 3 June 2019).
17 European Medicines Agency. Enbrel. Summary of product characteristics. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/enbrel (last accessed 3 June 2019).
18 Janssen. Stelara (ustekinumab). Package insert. Available at: http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/STELARA-pi.pdf (last accessed 3 June 2019).
19 European Medicines Agency. Stelara (ustekinumab). Summary of product characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf (last accessed 3 June 2019).
20 European Medicines Agency. Humira (adalimumab). Summary of product characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf (last accessed 3 June 2019).
21 Paller AS, Siegfried EC, Pariser DM *et al.* Long-term safety and efficacy of etanercept in children and adolescents with plaque psoriasis. *J Am Acad Dermatol* 2016; **74**:280–7.
22 Paller AS, Siegfried EC, Langley RG *et al.* Etanercept treatment for children and adolescents with plaque psoriasis. *N Engl J Med* 2008; **358**:241–51.
23 Landells I, Marano C, Hsu MC *et al.* Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: results of the randomized phase 3 CADMUS study. *J Am Acad Dermatol* 2015; **73**:594–603.
24 Bronckers I, Seyger MMB, West DP *et al.* Safety of systemic agents for the treatment of pediatric psoriasis. *JAMA Dermatol* 2017; **153**:1147–57.
25 Papp K, Thaci D, Marcoux D *et al.* Efficacy and safety of adalimumab every other week versus methotrexate once weekly in children and adolescents with severe chronic plaque psoriasis: a randomised, double-blind, phase 3 trial. *Lancet* 2017; **390**:40–9.
26 Fortina AB, Bardazzi F, Berti S *et al.* Treatment of severe psoriasis in children: recommendations of an Italian expert group. *Eur J Pediatr* 2017; **176**:1339–54.
27 Napolitano M, Megna M, Balato A *et al.* Systemic treatment of pediatric psoriasis: a review. *Dermatol Ther (Heidelb)* 2016; **6**:125–42.
28 Di Lernia V, Bonamonte D, Lasagni C *et al.* Effectiveness and safety of acitretin in children with plaque psoriasis: a multicenter retrospective analysis. *Pediatr Dermatol* 2016; **33**:530–5.
29 Dogra S, Mahajan R. Biologics in pediatric psoriasis – efficacy and safety. *Expert Opin Drug Saf* 2018; **17**:9–16.
30 Leonardi CL, Powers JL, Matheson RT *et al.* Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003; **349**:2014–22.
31 Gordon KB, Langley RG, Leonardi C *et al.* Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol* 2006; **55**:598–606.

32 Gottlieb AB, Chaudhari U, Mulcahy LD *et al.* Infliximab monotherapy provides rapid and sustained benefit for plaque-type psoriasis. *J Am Acad Dermatol* 2003; **48**:829–35.
33 Gottlieb AB, Evans R, Li S *et al.* Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2004; **51**:534–42.
34 Saurat JH, Stingl G, Dubertret L *et al.* Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol* 2008; **158**:558–66.
35 Burmester GR, Panaccione R, Gordon KB *et al.* Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann Rheum Dis* 2013; **72**:517–24.
36 Gordon K, Papp K, Poulin Y *et al.* Long-term efficacy and safety of adalimumab in patients with moderate to severe psoriasis treated continuously over 3 years: results from an open-label extension study for patients from REVEAL. *J Am Acad Dermatol* 2012; **66**:241–51.
37 Menter A, Thaci D, Papp KA *et al.* Five-year analysis from the ESPRIT 10-year postmarketing surveillance registry of adalimumab treatment for moderate to severe psoriasis. *J Am Acad Dermatol* 2015; **73**:410–19.
38 Kim GE, Seidler E, Kimball AB. Effect of age at diagnosis on chronic quality of life and long-term outcomes of individuals with psoriasis. *Pediatr Dermatol* 2015; **32**:656–62.
39 de Jager ME, de Jong EM, van de Kerkhof PC *et al.* An intrapatient comparison of quality of life in psoriasis in childhood and adulthood. *J Eur Acad Dermatol Venereol* 2011; **25**:828–31.
40 Warren RB, Kleyn CE, Gulliver WP. Cumulative life course impairment in psoriasis: patient perception of disease-related impairment throughout the life course. *Br J Dermatol* 2011; **164** (Suppl. 1):1–14.
41 Strober BE, Poulin Y, Kerdel FA *et al.* Switching to adalimumab for psoriasis patients with a suboptimal response to etanercept, methotrexate, or phototherapy: efficacy and safety results from an open-label study. *J Am Acad Dermatol* 2011; **64**:671–81.
42 Barker J, Hoffmann M, Wozel G *et al.* Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). *Br J Dermatol* 2011; **165**:1109–17.
43 Norlin JM, Steen Carlsson K, Persson U, Schmitt-Egenolf M. Switch to biological agent in psoriasis significantly improved clinical and patient-reported outcomes in real-world practice. *Dermatology* 2012; **225**:326–32.
44 Leonardi C, Papp K, Strober B *et al.* The long-term safety of adalimumab treatment in moderate to severe psoriasis: a comprehensive analysis of all adalimumab exposure in all clinical trials. *Am J Clin Dermatol* 2011; **12**:321–37.
45 Horneff G, Seyger MMB, Arikan D *et al.* Safety of adalimumab in pediatric patients with polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, psoriasis, and Crohn's disease. *J Pediatr* 2018; **201**:166–75.

Appendix

Funding sources

AbbVie Inc. funded this study and participated in the study design; study research; collection, analysis and interpretation of data; and writing, reviewing and approving of this publication. All authors had access to the data, and participated in the development, review and approval, and in the decision to submit this publication. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis datasets), as well as other information (e.g. protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. The clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and statistical analysis plan and execution of a data sharing agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing.html.

Conflicts of interest

D.T. has served as a consultant member of advisory boards for AbbVie, BMS, Celgene, Dignity, Galapagos, GlaxoSmithKline, Janssen-Cilag, Kymab, LEO Pharma, Lilly, Morphosis, Novartis, Regeneron, Samsung, Sandoz, Sanofi-Aventis, Pfizer and UCB; has served as a speaker for AbbVie, Almirall, Celgene, Janssen-Cilag, LEO Pharma, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, Sanofi-Aventis, Sun Pharma and UCB; and has participated as an investigator in clinical trials (for which the hospital has received support) for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Dignity, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Lilly, MedImmune, Merck Sharp & Dohme, Novartis, Regeneron, Sandoz, Sanofi-Aventis, Takeda, Pfizer and UCB. K.P. has received honoraria for participation on advisory boards or panels, and as a consultant and speaker, from AbbVie, Active Biotech, Akesis, Allergan, Amgen, Anacor, Astellas, AstraZeneca, Basilea, Baxter, Bayer, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, CanFite, Cato, Cepheid, Celgene, Centocor, Cipher, Coherus, Dow Pharma, Eli Lilly, Endocyte, Ferring Pharma, Forward Pharma, Galderma, Genentech, Gilead, GlaxoSmithKline, Janssen, Kyowa Hakko Kirin, Kythera, LEO Pharma, MedImmune, Meiji Seika Pharma, Merck Sharp & Dohme, Merck Serono, Mylan, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Rigel, Roche, Sanofi-Genzyme, Sosei, Sun Pharma, Takeda, UBC, Vertex and Wyeth; and has received grants as an investigator from AbbVie, Active Biotech, Akesis, Allergan, Amgen, Anacor, Astellas, AstraZeneca, Basilea, Baxter, Bayer, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, CanFite, Cato, Celgene, Centocor, Cepheid, Cipher, Coherus, Dow Pharma, Eli Lilly, Endocyte, Ferring Pharma, Forward Pharma, Galderma, Genentech, Gilead, GlaxoSmithKline, Janssen, Kyowa Hakko Kirin, Kythera, LEO Pharma, MedImmune, Meiji Seika Pharma, Merck Sharp & Dohme, Merck Serono, Mylan, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Rigel, Roche, Sanofi-Genzyme, Sosei, Sun Pharma, Takeda, UBC, Vertex and Wyeth.

D.M. has received honoraria from AbbVie, Johnson & Johnson, Pierre Fabre and Galderma for advisory board, consultant and speaker services; and grants from Celgene, Eli Lilly, LEO, Novartis and Sanofi Regeneron for investigator services. L.W. has received honoraria from AbbVie for participation as an investigator of this study, from Novartis for investigator services, and from Pierre Fabre, Meda, Merz, Sanofi and Pfizer for participation on ad boards, as a speaker and for consultancy. A.P. has worked as an investigator and/or speaker and/or advisor for AbbVie, Almirall, Amgen, Biogen, BMS GmbH, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen-Cilag, GSK, LEO, MSD, Maruho, Medac, Novartis, Pascoe, Pfizer, Pierre Fabre, Roche, Sanofi-Aventis, Tigercat and UCB Pharma. P.D.G. has received honoraria from AbbVie, Amgen, BMS, Celgene, Eli Lilly, Fien, Galderma, Janssen, LEO, Maruho, Meda, MSD, Novartis, Pfizer and UCB for participation as a consultant, investigator or speaker, and for participation on ad boards. I.L. has received honoraria from AbbVie, Amgen, Celgene, Eli Lilly, Janssen, LEO Pharma, Merck Serono and Valeant for participation as a consultant, investigator or speaker, and for participation on ad boards. P.H.H. has received honoraria for investigator services from AbbVie, Pierre Fabre and Janssen, and for advisory board, consultant and speaker services from Infectopharm, Pierre Fabre, GSK and Almirall. K.U., S.R. and D.A.W. receive a salary as AbbVie employees, and may also own AbbVie stock or stock options. M.M.B.S. has received grants from and was involved in clinical trials with AbbVie, Almirall, Astellas, Janssen, Eli Lilly, LEO Pharma and Pfizer; has served as a consultant for AbbVie, Almirall, Boehringer Ingelheim, Janssen, Lilly and Pfizer; has served as a speaker for Pfizer; and has received honoraria for travel with AbbVie, Pfizer and LEO Pharma; fees were paid directly to the institution. S.P. has received honoraria or grants for speaker services from AbbVie, Almirall, Amgen, Biogen, BMS GmbH, Boehringer Ingelheim, Celgene, Janssen-Cilag, MSD, Mundipharma, Novartis and UCB Pharma; for advisory board services from AbbVie, Biogen, Eli Lilly, Janssen-Cilag, LEO Pharma, Pfizer, MSD and Novartis; and for investigator services from AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly, GSK, Janssen-Cilag, LEO Pharma, Maruho, MSD, Novartis, Pfizer, UCB Pharma and VBL Therapeutics.