CLINICAL TRIAL

BJD
British Journal of Dermatology

Efficacy and safety of fumaric acid esters in young patients aged 10–17 years with moderate-to-severe plaque psoriasis: a randomized, double-blinded, placebo-controlled trial*

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Linked Comment: B. Volc-Platzer. *Br J Dermatol* 2021; **185**:5–6.

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Accepted for publication
12 December 2020

Funding sources
This study was funded by Biogen GmbH, Munich, Germany

Conflicts of interest
H.H., as an employee of the University Hospital Würzburg, received honoraria for his institution from Biogen GmbH as coordinating investigator of the clinical trial. He has also received speaker's honoraria or travel expense reimbursements from and/or received grants from and/or participated in clinical trials for AbbVie, Allergika, Beiersdorf, Celgene, InfectoPharm, LEO, med update, Novartis and Pierre Fabre. D.W.-T. has been an advisor for and/or received speaker's honoraria or travel expense reimbursements from and/or received grants from and/or participated in clinical trials for AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim Pharma, Celgene, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO, Lilly, Medac, Merck Sharp & Dohme Corp., Novartis, Pfizer, UCB Pharma and VBL. A.T. was an investigator for the clinical trial. T.G., as an employee of the University Hospital St Josef Hospital (Bochum), has received speaker's and/or advisory board honoraria from BMS, Sanofi Genzyme, MSD, Novartis, Roche, AbbVie, Almirall, Janssen, Lilly, Pfizer, Pierre Fabre and Biogen, outside the

Summary

Background Apart from biologics, no systemic drugs are approved in Europe for children with moderate-to-severe psoriasis. Retrospective observational studies have shown promising results for fumaric acid esters (FAE) in this setting.
Objectives To show superiority of FAE over placebo in terms of treatment response after 20 weeks in children and adolescents aged 10–17 years.
Methods In a multicentre, randomized, double-blind, placebo-controlled phase IIIb study, patients aged 10–17 years with moderate-to-severe plaque psoriasis requiring systemic therapy were randomized 2 : 1 to receive FAE (n = 91) or placebo (n = 43) over 20 weeks, followed by an open-label FAE treatment phase. The coprimary endpoints were ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75) and Physician's Global Assessment (PGA) score of 0 or 1 (clear or almost clear) at week 20. The study was registered with EudraCT number 2012-000035-82.
Results At week 20, 55% [95% confidence interval (CI) 0·44–0·65] of FAE-treated patients achieved a PASI 75 response vs. 19% (95% CI 0·08–0·33) in the placebo group (absolute difference 36%, 95% CI 0·20–0·53; $P < 0·001$). In total, 42% (95% CI 0·32–0·53) in the FAE group vs. 7% (95% CI 0·01–0·19) in the placebo group achieved a PGA score of 0 or 1 at week 20 (absolute difference 35%, 95% CI 0·21–0·49; $P < 0·001$). During the double-blind period, drug-related adverse events occurred more frequently in patients receiving FAE compared with placebo (76% vs. 47%). Gastrointestinal disorders were the most common adverse events.
Conclusions FAE administered over a period of 20 weeks demonstrated a better response than placebo; the difference was statistically significant and clinically meaningful. Application up to 40 weeks was generally well tolerated. However, further studies are required.

What is already known about this topic?

- Fumaric acid esters (FAE) are recommended by the 2015 European evidence-based S3-guidelines on psoriasis treatment as a systemic option for moderate-to-severe plaque psoriasis in adults.

submitted work. K.T., J.L., U.F. and C.M. are employees of Biogen.

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*Plain language summary available online

DOI 10.1111/bjd.19747

- FAE are effective in adult patients with psoriasis and have a favourable long-term safety profile.

What does this study add?

- This is the first randomized controlled trial conducted with FAE in children and adolescents aged 10–17 years with moderate-to-severe plaque psoriasis requiring systemic treatment.
- FAE are effective in children and adolescents.

Psoriasis is a common systemic inflammatory disease affecting people of all age groups. Although the peak onset occurs in early adulthood between the age of 20 and 30 years, psoriasis is also common among adolescents and children.[1–3] A prevalence of 0·71% has been reported for German children and adolescents aged up to 18 years.[4] In line with national healthcare objectives aimed at improving physical and mental symptoms and minimizing potential negative long-term effects on future health and psychosocial development, early recognition and treatment of paediatric psoriasis are considered to be particularly important.[3,5] However, treating children with moderate-to-severe psoriasis is challenging. At the time this study was initiated, etanercept was the only biological agent authorized for use in children with plaque psoriasis.

Data regarding the benefits and risks of conventional systemic treatments such as acitretin, methotrexate and ciclosporin in paediatric patients are sparse for this indication and largely derive from studies in young patients with indications other than psoriasis.[6] Methotrexate and ciclosporin are the most cost-effective, but they are not recommended for long-term treatment, because of high potential for long-term toxicity. Moreover, they are not approved for children and adolescents with psoriasis in Europe. Acitretin has limited efficacy as monotherapy, and side-effects such as teratogenicity and interference with bone metabolism may restrict its use in paediatric patients.[7] In the European Union, approval of paediatric systemic therapeutic options is currently limited to five biologics (etanercept, adalimumab, ustekinumab, secukinumab and ixekizumab), of which etanercept and ustekinumab are second-line options.[8–12] Biologics are relatively novel pharmacological agents and long-term safety and efficacy data are limited.[13] Therefore, many practitioners prefer the use of established medications that have been approved for children and adolescents with other indications such as juvenile arthritis and Crohn disease, and in the post-organ transplant setting.[14–18]

Fumaric acid esters (FAE) are one of the most commonly used systemic antipsoriatic drugs in many countries, but approval is restricted to treatment of adults.[19] Also, a recently approved dimethyl fumarate (DMF) monotherapy for moderate-to-severe psoriasis was approved only for adults.[20–22] These small molecules have been shown to improve psoriasis by a broad range of immunomodulatory effects.[23] Although the use of FAE in the paediatric psoriasis population is off-label, there are numerous case reports and case series besides unpublished clinical experience to suggest that FAE may be an effective treatment option for children and adolescents if a systemic therapy is indicated.[7,24–27]

Based on these experiences, the 2019 published German guidelines state that FAE may be recommended for moderate-to-severe psoriasis in children and adolescents who are inadequately controlled by, or are intolerant to adalimumab or methotrexate, or when these agents are contraindicated.[28] Fumaderm® is a mixture of different FAEs: DMF and three salts of ethyl hydrogen fumarate (EHF salts).[29] Retrospective studies underlined the favourable efficacy and safety, as well as a very low drug–drug interaction potential with long-term use in adult populations.[30,31] After single case reports and a small retrospective study showed promising efficacy and safety in patients younger than 18 years,[7,24,32,33] a retrospective data collection evaluated the use of FAE in children and adolescents for up to 60 months. The data obtained suggested that long-term FAE therapy in this patient group may be safe and effective.[34] To verify these results, the present clinical study was conducted. The main objective of this trial was to assess the efficacy and safety of FAE vs. placebo in patients aged 10–17 years after 20 weeks of treatment.

Patients and methods

Trial design

This multicentre, randomized, double-blinded, placebo-controlled phase IIIb study was conducted in concordance with

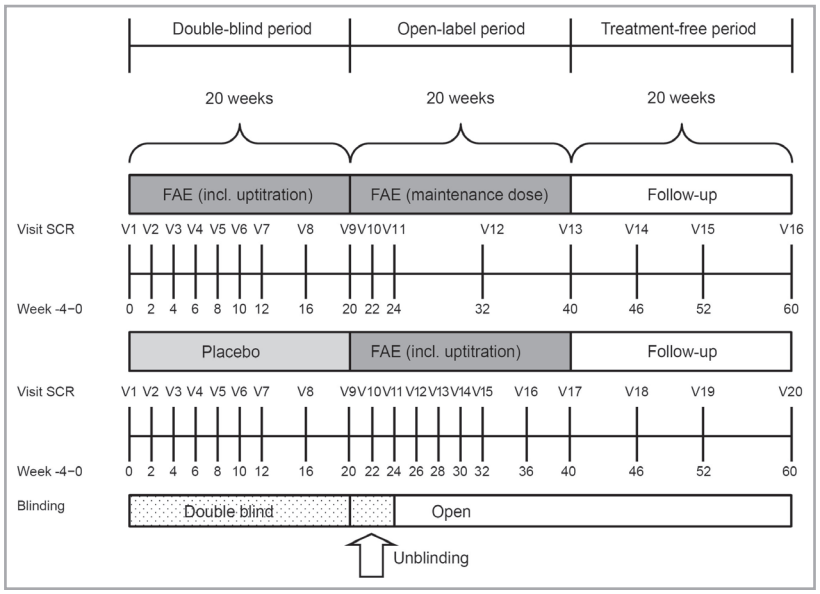

Figure 1 Study design. FAE, fumaric acid esters; SCR, screening.

the ethical principles of the Declaration of Helsinki at 22 sites in Germany from December 2012 to September 2016. Eligible patients were randomized 2 : 1 to treatment arm A (FAE) or treatment arm B (placebo). After a 20-week double-blind period, all patients were switched to FAE for 20 weeks. Patients then entered a 20-week treatment-free safety follow-up period. The trial protocol was reviewed and approved by the independent ethics committee of the Medical Faculty of Julius-Maximilians-Universität Würzburg (reference no. 109/12_ff). The trial is registered at the European Clinical Trials Database (EudraCT no. 2012-000035-82).

Participants

To be eligible for participation, male and female patients aged 10–17 years had to fulfil the following criteria. (i) A diagnosis of moderate-to-severe plaque psoriasis according to the rule of ten [Psoriasis Area and Severity Index (PASI) ≥ 10, or ≥ 10% involved body surface area (BSA), or Children's Dermatology Life Quality Index (CDLQI)/Dermatology Life Quality Index (DLQI) ≥ 10]; the European consensus of treatment goals for moderate-to-severe psoriasis; and history of plaque psoriasis for at least 6 months if previous, externally applied, standalone treatments had failed. (ii) A need for systemic treatment: moderate-to-severe forms of plaque psoriasis in cases where previous, externally applied, standalone treatments had failed. (iii) Weight > 30 kg. (iv) Signed informed consent (by patient and parents). A complete list of inclusion and exclusion criteria is available in Appendix S1 (see Supporting Information). Data were collected from 22 dermatological sites (hospitals and outpatient centres) involved in the diagnosis and care of patients with psoriasis in Germany.

Interventions

The clinical study consisted of a 20-week double-blind treatment period, which was followed by a 40-week open-label period, consisting of a 20-week treatment period and a subsequent 20-week treatment-free follow-up period (Figure 1). In the double-blind period, patients received either FAE tablets or matching placebo. Uptitration was performed starting at 30 mg DMF and 75 mg EHF salts daily (equalling one tablet of Fumaderm Initial), with an incremental increase as per the Summary of Product Characteristics (SmPC),[29] but with the exception of a maximum daily dosage of 480 mg DMF and 380 mg EHF salts (equalling four tablets of Fumaderm) based on individual clinical response and tolerability. From week 20 to week 40, patients receiving FAE maintained the dose of FAE they received at the end of the first 20-week period (FAE/FAE group). Patients on placebo received uptitrated FAE from week 20 to 40 (placebo/FAE group). From week 40 to week 60, all patients were in the treatment-free follow-up period. Over the entire study period, no usage of cosmetic products or procedures was allowed, except for basic skincare (Basiscreme DAC; Bombastus-Werke AG, Freital, Germany).

Outcomes

The two coprimary outcome measures for treatment efficacy were (i) the percentage of patients who exhibited ≥ 75% reduction of PASI (PASI 75 responder rate) and (ii) the percentage of patients rated to be 'clear' or 'almost clear' according to the Physician's Global Assessment (PGA 0 or 1) after 20 weeks of randomized treatment. Secondary outcome measures for treatment effectiveness were assessed at all visits and included PASI means; PASI 50, 75 and 90; PGA; and CDLQI/DLQI. Adverse

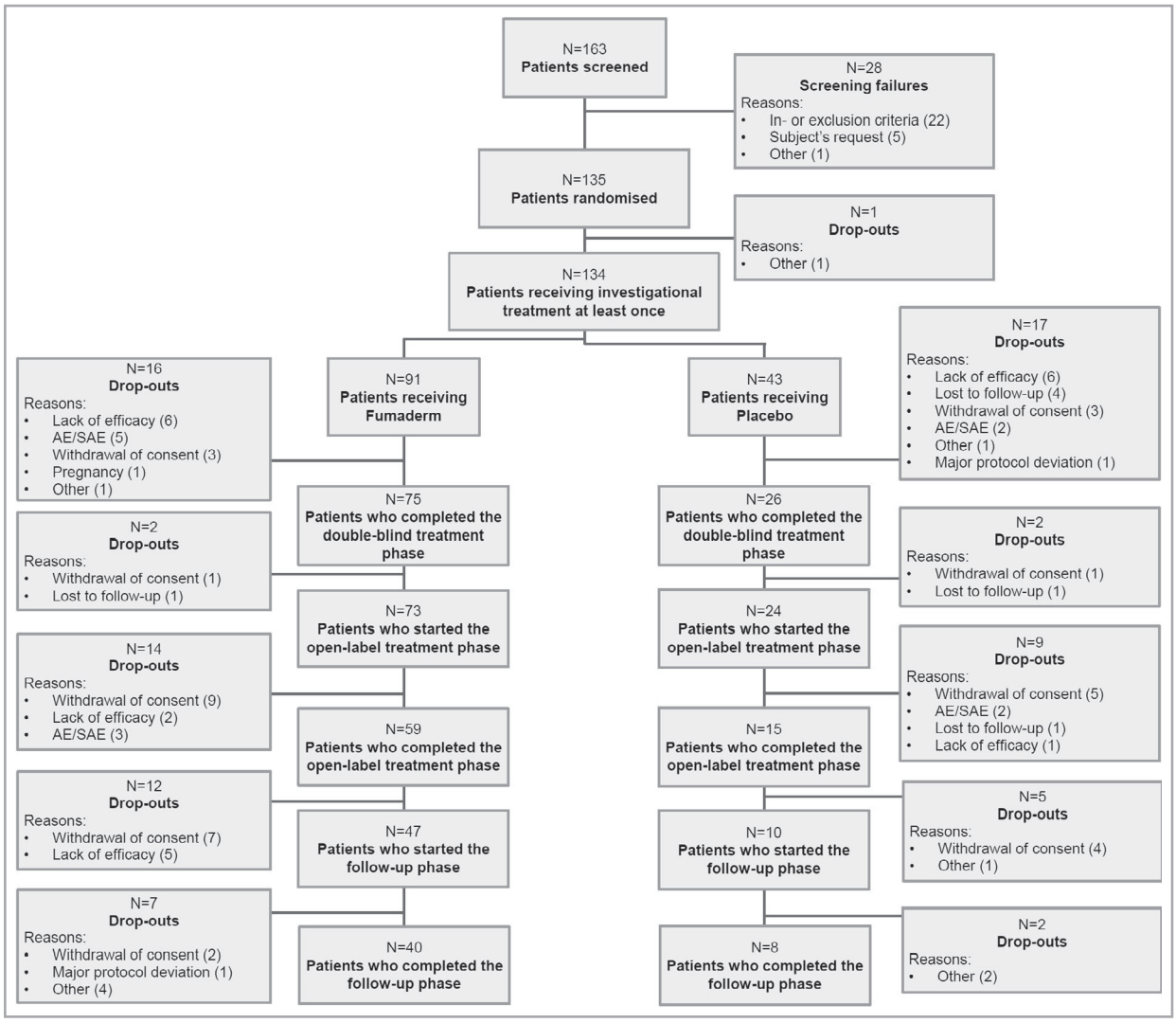

Figure 2 Patient flow. AE, adverse event; SAE, serious adverse event.

events (AEs), serious AEs (SAEs) and laboratory values were recorded at all study visits and served as endpoints for the assessment of safety. Exploratory, not predefined endpoints included duration of remission and time to relapse and rebound (post hoc analysis), as previously defined (Appendix S1).[35]

Sample size

A sample size of 133 patients was planned for this study. A detailed description of how the sample size was derived is available in Appendix S1.

Randomization and blinding

Using computer-generated randomization lists, patients were randomly allocated in a ratio of 2 : 1 to treatment arm A (FAE/FAE) or treatment arm B (placebo/FAE). Treatment assignment was unbiased and concealed from patients and investigational site staff. During the double-blind period, the investigational product and the respective comparator were indistinguishable in packaging, labelling, appearance, consistency, odour and schedule of administration up to week 20. At week 20, a study nurse not otherwise involved in the study was unblinded for adequate dispense of the study medication. At week 24, the investigators, further blinded study personnel and patients were unblinded.

Statistical methods

Efficacy endpoints were assessed for the full analysis set, consisting of all randomized patients who had received at least one dose of study drug. Replacement of missing values was performed for the two coprimary endpoints (the primary analysis timepoint was week 20: the end of the double-blind treatment period) using the last observation carried forward method. In order to show robustness of the results, a worst-case approach was applied in a post hoc sensitivity analysis of the coprimary endpoints, defining early dropout as nonresponse. For each

Table 1 Patient demographics and baseline characteristics

Parameter	FAE, n = 91	Placebo, n = 43	Total, n = 134
Age (years), mean (SD)	14·2 (2·1)	13·9 (2·4)	14·1 (2·2)
Age group, n (%)			
10 to < 12 years	14 (15)	9 (21)	23 (17·2)
12 to < 14 years	17 (19)	10 (23)	27 (20·1)
14 to 17 years	60 (66)	24 (56)	84 (62·7)
Sex, n (%)			
Male	51 (56)	24 (56)	75 (56·0)
Female	40 (44)	19 (44)	59 (44·0)
BMI (kg m^{-2}), mean (SD)	22·0 (4·4)	23·6 (5·4)	22·6 (4·8)
BMI groups, n (%)			
Underweight	3 (3)	1 (2)	4 (3·0)
Healthy weight	60 (66)	22 (51)	82 (61·2)
Overweight	18 (20)	13 (30)	31 (23·1)
Obese	10 (11)	7 (16)	17 (12·7)
Duration of psoriasis (years), mean (SD)	4·8 (4·1)	4·7 (3·6)	4·8 (3·9)
Psoriasis previously treated, n (%)	87 (96)	40 (93)	127 (94·8)
Affected BSA (%), mean (SD)	27·8 (17·3)	28·4 (17·8)	28·0 (17·4)
PGA, mean (SD)	4·4 (0·8)	4·3 (0·8)	4·4 (0·8)
PASI, mean (SD)	16·8 (7·5)	16·0 (7·3)	16·5 (7·4)
CDLQI, mean (SD); N	10·1 (6·7); 78	9·6 (7·0); 34	9·9 (6·7); 112
DLQI, mean (SD); N	9·2 (3·8); 14	10·4 (6·4); 9	9·7 (4·9); 23
Medical history (incidence > 5%)			
Acne	9 (10)	0 (0)	9 (6·7)
Asthma	4 (4)	4 (9)	8 (6·0)
Headache	4 (4)	3 (7)	7 (5·2)
Obesity	5 (5)	2 (5)	7 (5·2)

BMI, body mass index; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index (used for children aged 10–16 years); DLQI, Dermatology Life Quality Index (used for children aged 17 years); FAE, fumaric acid esters; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment.

coprimary endpoint, the responder rates of FAE and placebo were compared using Fisher's exact test. The 95% confidence intervals (CIs) for the rates were calculated according to Clopper and Pearson. The absolute (risk) differences of the responder rates were calculated with corresponding 95% CIs. As a further post hoc sensitivity analysis, a combined endpoint based on PASI 75 and PGA (0,1), was defined and analysed. Combined response was defined as PASI 75 and PGA (0,1) response. For the FAE/FAE group, the visit of randomization and first FAE dosing was used for all following visits.

Results

Patients

In total, 163 patients were screened. After excluding 28 patients due to screening failures, 135 patients were randomized. Of these, 134 patients received the blinded study drug at least once and comprised the safety and full analysis set. In total 101 patients completed the double-blind period (20 weeks). Among the 97 patients who entered the open-label period, 48 patients completed the study through week 60 (Figure 2). The patient demographics and baseline characteristics were comparable between the treatment groups (Table 1). Almost all patients had received prior therapies for psoriasis (98% in each group). Topical vitamin D3 analogues and corticosteroids were used most frequently, and nine patients had received a prior immunosuppressive therapy (Table 2).

Table 2 Any prior and concomitant therapy taken or started up to 6 months prior to randomization as per ATC code level 3 (adapted) (reported for > 5% of patients)

Therapy, n (%)	FAE, n = 91	Placebo, n = 43
Topical		
Antipsoriatics for topical use	69 (76)	28 (65)
Topical vitamin D analogues	58 (64)	26 (60)
Topical corticosteroids, plain	62 (68)	29 (67)
Emollients and protectives	18 (20)	9 (21)
Topical corticosteroids, other combinations	11 (12)	3 (7)
Other topical dermatological preparations	8 (9)	5 (12)
Antifungals for topical use	4 (4)	3 (7)
Systemic		
Hormonal contraceptives for systemic use	10 (11)	3 (7)
Antihistamines for systemic use	6 (7)	3 (7)
Immunosuppressants for systemic use	6 (7)	3 (7)
All other nontherapeutic products	10 (11)	3 (7)

ATC, World Health Organization Anatomical Therapeutic Chemical code for medicines; FAE, fumaric acid esters.

Table 3 New drug therapies (including treatments of adverse events) started during the study as per ATC code level 3 (reported for > 5% of patients)

Therapy, n (%)	FAE/FAE, n = 91	Placebo/FAE, n = 43
Double-blind period		
Anti-inflammatory and antirheumatic products, nonsteroids	22 (24)	11 (26)
Other analgesics and antipyretics	16 (18)	12 (28)
Antihistamines for systemic use	12 (13)	9 (21)
Hormonal contraceptives for systemic use	12 (13)	3 (7)
Antipsoriatics for topical use[a]	7 (8)	7 (16)
Expectorants, excluding combinations with cough suppressants	6 (7)	7 (16)
Corticosteroids, plain	6 (7)	6 (14)
Drugs for peptic ulcer and GORD	6 (7)	3 (7)
Emollients and protectives	5 (5)	4 (9)
Adrenergics, inhalants	5 (5)	3 (7)
Other beta-lactam antibacterials	5 (5)	3 (7)
Decongestants and other nasal preparations for topical use	4 (4)	6 (14)
Throat preparations	4 (4)	4 (9)
Open-label + treatment-free period		
Anti-inflammatory and antirheumatic products, nonsteroids	16 (18)	7 (16)
Other analgesics and antipyretics	15 (16)	5 (12)
Hormonal contraceptives for systemic use	10 (11)	1 (2)
Expectorants, excluding combinations with cough suppressants	8 (9)	3 (7)
Corticosteroids, plain	7 (8)	0 (0)
Systemic antipsoriatics[a]	6 (7)	3 (7)
Emollients and protectives	6 (7)	1 (2)
Antihistamines for systemic use	5 (5)	5 (12)
Anti-acne preparations for topical use	5 (5)	2 (5)
Drugs for peptic ulcer and GORD	5 (5)	2 (5)

ATC, World Health Organization Anatomical Therapeutic Chemical code for medicines; FAE, fumaric acid esters; GORD, gastro-oesophageal reflux disease. [a]Use of concomitant antipsoriatics during the study was regarded as major protocol deviation; these patients were excluded from the per protocol set.

Treatment

The mean exposure to DMF, an active ingredient of Fumaderm, was 301 ± 103 mg per day during weeks 5–40 in the FAE/FAE group and 288 ± 138 mg per day during weeks 25–40 in the placebo/FAE group. The first 4 weeks were required for uptitration. During the double-blind period, in total 244 concomitant therapies were reported for 73 patients (80%) in the FAE group, and 186 concomitant therapies were reported for 34 patients (79%) in the placebo group (Table 3). Anti-inflammatory and antirheumatic products were used most frequently.

Efficacy outcomes

Responder rates for ≥ 75% improvement in Psoriasis Area and Severity Index and Physician's Global Assessment (o,1) (coprimary endpoints)

The rates of patients with PASI 75 receiving FAE or placebo at week 20 were respectively 0·55 (95% CI 0·44–0·65) and 0·19 (95% CI 0·08–0·33). The absolute difference between the responder rates was statistically significant (0·36, 95% CI 0·20–0·53; $P < 0·001$) (Figure 3a). The rate of patients with PGA assessed as clear (score 0) or almost clear (score 1) was also greater in the FAE group (0·42, 95% CI 0·32–0·53) compared with placebo (0·07, 95% CI 0·01–0·19) at week 20. The absolute difference between the responder rates was 0·35 (95% CI 0·21–0·49; $P < 0·001$) (Figure 3b). Concordantly, the rate of patients reaching the combined endpoint of PASI 75 and PGA (0,1) was 0·40 (95% CI 0·29–0·50) for FAE and 0·07 (95% CI 0·01–0·19) for placebo (absolute difference 0·33, 95% CI 0·19–0·46; $P < 0·001$).

Secondary endpoints

In the FAE/FAE group, the mean PASI decreased until week 24 (mean 2·7, SD 3·0; end of the double-blind treatment period), stayed more or less the same through week 32 (mean 2·4, SD 2·5) and then slightly increased again to week 60 (mean 5·2, SD 5·2) (Figure 4). In the placebo/FAE group, a decrease of the mean PASI until week 20 was also observed (mean 9·2, SD 11·7), but the decrease was considerably less than in the FAE/FAE group (mean 3·5, SD 3·8). At week 40, namely after the first 20 weeks of treatment with FAE in the placebo/FAE group, a decrease of the mean PASI was observed (mean 2·5, SD 1·9). At week 60, the mean PASI had then slightly increased again (mean 3·6, SD 3·9). PASI 50, PASI 75

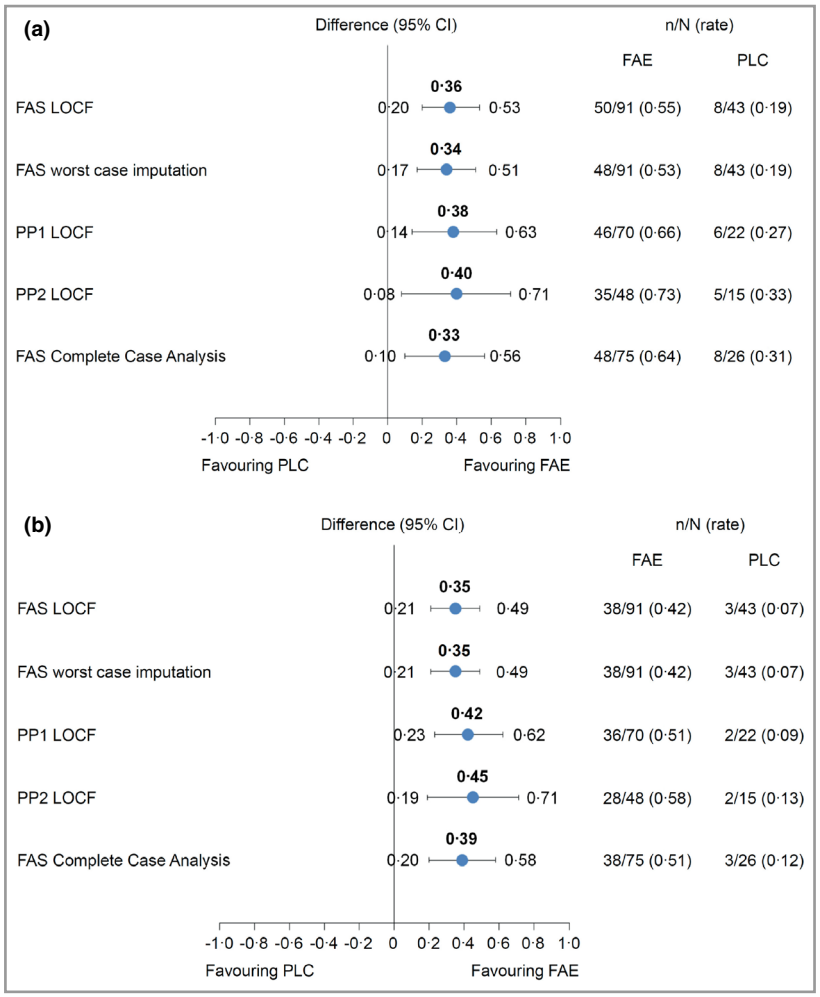

Figure 3 Forest plots showing the coprimary endpoints – responder rates of (a) ≥ 75% improvement in Psoriasis Area and Severity Index (PASI) and (b) Physician's Global Assessment score of 0 or 1 at week 20. FAS, full analysis set: all randomized patients who received the investigational treatment at least once. PP1: all patients who received the investigational treatment at least once, whose primary endpoint (PASI and/or PGA at week 20) was available and who completed the study up to and including visit 9 (week 20, i.e. end of study phase 1) without any major protocol deviations. PP2: all patients who received the investigational treatment at least once, whose primary endpoint (PASI and/or PGA at week 20) was available and who completed the study without any major protocol deviations. A complete-case analysis was performed as a post hoc sensitivity analysis for both primary endpoints based on the FAS. Both analyses supported the confirmatory analysis. Robustness of the results was shown by comparing the responder rates for FAS, PP1, and PP2 with the responder rates based on the worst-case imputation approach. CI, confidence interval; FAE, fumaric acid esters; LOCF, last observation carried forward; PLC, placebo.

and PASI 90 responder rates in the double-blind period are presented in Table S1 (see Supporting Information).

The PGA (0,1) responder rate increased over time in the FAE/FAE group until week 24 (41 patients, 45%), stayed more or less the same at week 32 and then decreased until week 60 (10 patients, 11%) (Figure 5). In the placebo/FAE group, an increase of the PGA (0,1) responder rate until week 20 was also observed (three patients, 7%), but the increase was considerably lower than in the FAE/FAE group (38 patients, 42%). Until week 40, namely in the first 20 weeks of treatment with FAE in the placebo/FAE group, an increase of the PGA (0,1) responder rate was observed (six patients, 14%). Up to week 60, the responder rate stayed more or less the same (five patients, 12%).

The mean CDLQI followed a similar pattern over time as observed for PASI and PGA (Figure 6). The 17-year-old patients completing the DLQI showed a similar course (data not shown).

Post hoc analysis of the exploratory endpoints remission and relapse showed no statistically significant differences between the treatment groups (Figures S1 and S2; see Supporting Information) and there was only one patient experiencing a rebound in the FAE/FAE group at week 20.

Safety outcomes

During the double-blind period, in total 470 AEs were reported in 84 patients in the FAE group, and 169 AEs were

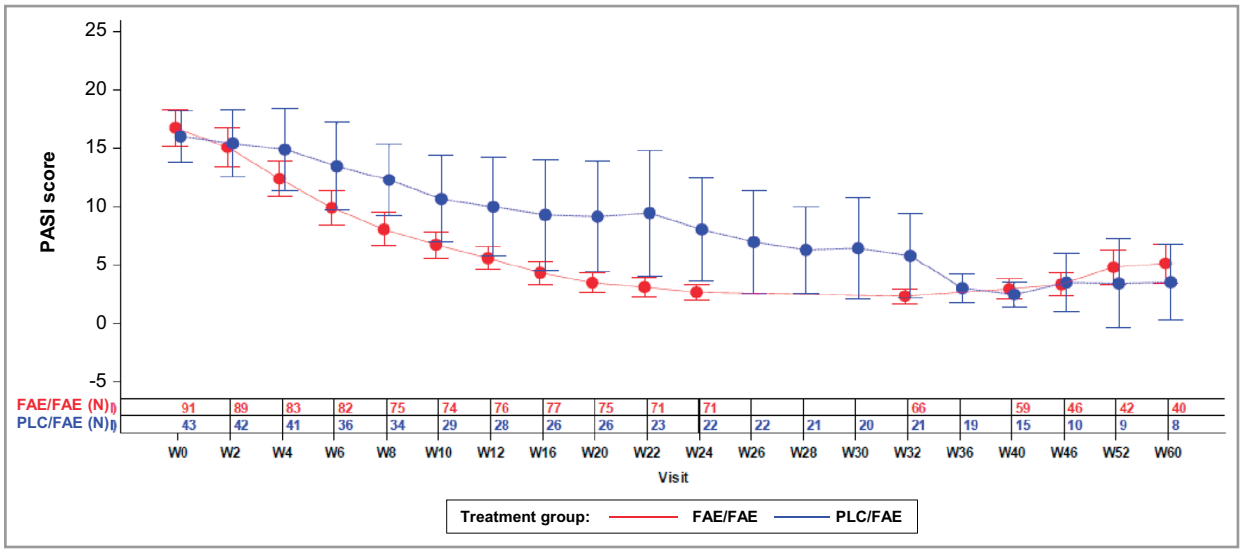

Figure 4 Mean Psoriasis Area and Severity Index (PASI) over time, with 95% confidence intervals (CIs). No visits were performed in the FAE/FAE group at weeks 26–30 and 36. FAE, fumaric acid esters; PLC, placebo.

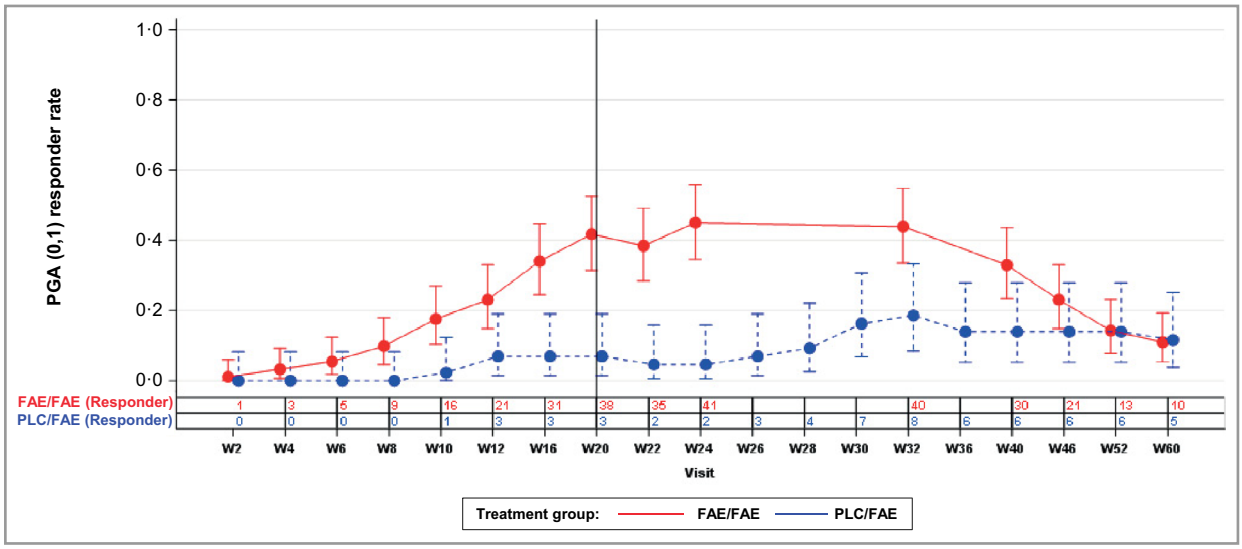

Figure 5 Responder rates for Physician's Global Assessment (PGA) score of 0 or 1 over time, with 95% confidence intervals (CIs). No visits were performed in the FAE/FAE group at weeks 26–30 and 36. FAE, fumaric acid esters; PLC, placebo.

reported in 37 patients in the placebo group (Table 4). Of those, 279 AEs in 69 patients receiving FAE and 55 AEs in 20 patients receiving placebo were judged to be related to the study medication. Most events reported were mild (FAE, 77 patients; placebo, 31 patients); severe drug-related AEs were reported for 11 patients in the FAE group and two patients in the placebo group. AEs leading to permanent study discontinuation were reported in six and three patients in the FAE and placebo groups, respectively. Gastrointestinal disorders occurred more frequently in the FAE group than in the placebo group.

During the open-label and treatment-free period, 227 AEs were reported in 59 patients in the FAE/FAE group and 118 AEs were reported in 23 patients in the placebo/FAE group (Table 4). Of those, 90 AEs in 34 patients in the FAE/FAE group and 74 AEs in 18 patients in the placebo/FAE group were judged to be related to the study medication. The most frequently reported AE in the open-label and treatment-free period was nasopharyngitis in the FAE/FAE group. Most AEs in the open-label and treatment-free period were of mild intensity (FAE/FAE, 51 patients; placebo/FAE, 21 patients).

In total, 27 SAEs were reported in 21 patients during the study (Table 4). In one 17-year-old male patient severe reversible drug-induced liver injury (DILI) was observed (see Appendix S1 for a case narrative). FAE (three tablets per day) were discontinued after 4 months. Hepatic transaminases and bilirubin elevated to > 3 times the upper limit of normal and > 2 times the upper limit of normal, respectively, and

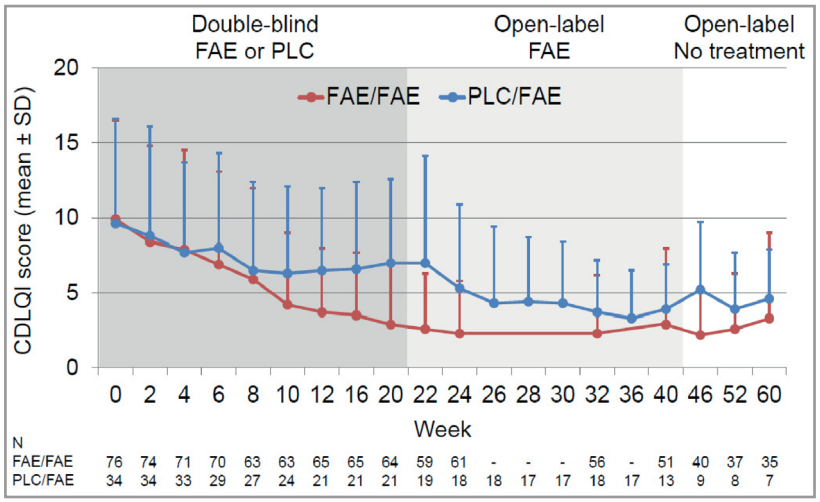

Figure 6 Children's Dermatology Life Quality Index (CDLQI) over time. No visits were performed in the FAE/FAE group at weeks 26–30 and 36. Only patients aged 10–16 years are included. Patients aged 17 years used the Dermatology Life Quality Index. FAE, fumaric acid esters; PLC, placebo.

reversed following withdrawal of treatment. Supportive histopathological findings were also consistent with DILI. One patient in the FAE group experienced severe proteinuria during the double-blind period (see Appendix S1 for a case narrative). Other SAEs were worsening of the underlying psoriasis (n = 3) or gastrointestinal in nature (n = 2), or single occurrences of accidents or injuries or common diseases. One patient had spontaneous abortion.

Discussion

To our knowledge, this was the first randomized controlled trial conducted with FAE in children and adolescents aged 10–17 years with moderate-to-severe plaque psoriasis requiring systemic treatment, which is the primary indication for FAE in adults.[29] The mean PASI of 16·5, mean PGA of 4·4, mean affected body surface of 28%, and mean CDLQI (DLQI) of 9·9 (9·7) indicate at least moderate disease burden at baseline. Efficacy of FAE was shown in the double-blind period and was maintained over an additional 20 weeks in the open-label treatment period. Over the treatment course, FAE led to significant improvement of psoriasis as evidenced by reductions in PASI, PGA and CDLQI/DLQI. Efficacy was evaluated by use of standard parameters that are well described in guidelines and widely used in clinical testing of drugs intended for use in psoriasis.[36]

The primary objective of this study was to assess the efficacy and safety of FAE treatment after 20 weeks compared with placebo. For this purpose, the study had two coprimary efficacy endpoints: the rate of patients with PASI 75 and the rate of patients with PGA assessed as clear or almost clear (PGA 0 or 1). The statistical analyses of the full analysis set showed that FAE are statistically significantly superior to placebo for both coprimary endpoints. A post hoc analysis of the combined coprimary endpoints confirmed the result of the single analyses with statistical significance. The worst-case analysis, which considered all dropouts as nonresponders, underlined the robustness of the results.

Secondary variables for patients randomized to the FAE/FAE group were consistent with results for the primary variables after 20 weeks of treatment and showed a consistent course over the study period with improving results during the double-blind treatment period, a plateau during the open-label treatment period and a tendency for deterioration during the treatment-free period. As expected in the area of dermatological diseases,[37] patients randomized to the placebo group also showed improvement during the double-blind treatment period, which remained at a low level. The improvements in PASI and PGA corroborated observations from the retrospective data collection.[34] Patients in our study had similar mean PASI at baseline, but higher PGA and larger affected skin areas compared with those from the retrospective data collection.[28]

During the double-blind treatment period, AEs occurred more frequently in the FAE group, as expected. Generally, AEs primarily involved gastrointestinal symptoms and flushing.[34] Compared with the double-blind period, gastrointestinal disorders occurred less commonly in the open-label and treatment-free period, with a slightly higher percentage of patients with gastrointestinal disorders in the placebo/FAE group, indicating that there are fewer gastrointestinal AEs when patients had been on FAE for some time, compared with when FAE treatment was started. In this study some AEs, such as upper abdominal pain and nausea, occurred more frequently in children than outlined in the SmPC, which is based on adult populations.[29] However, bearing in mind the high rate of events (> 10%) witnessed in the placebo arm, caution is advised in comparing the absolute incidence rate in the FAE-treated group with that detailed in the SmPC. The data indicate that overall the safety profile in children is consistent with that in the adult population. At the time of the trial, DILI was not a known side-effect of Fumaderm. Based on analysis of the data, DILI will be included in the safety profile of Fumaderm in the SmPC.

Table 4 Overview of patients with adverse events (AEs)

	Double-blind period		Open-label + treatment-free period	
Number (%) of patients	FAE, n = 91	Placebo, n = 43	FAE/FAE, n = 91	Placebo/FAE, n = 43
Any AEs	84 (92)	37 (86)	59 (65)	23 (53)
Drug-related AEs	69 (76)	20 (47)	34 (37)	18 (42)
AEs leading to permanent study drug discontinuation[a]	6 (7)	3 (7)	3 (3)	2 (5)
Any SAE	9 (10)	3 (7)	7 (8)	2 (5)
Drug-related SAEs	3 (3)	0 (0)	2 (2)	1 (2)
AEs with > 5% incidence[b]				
Nasopharyngitis	37 (41)	15 (35)	29 (32)	9 (21)
Flushing	33 (36)	5 (12)	15 (16)	9 (21)
Upper abdominal pain	27 (30)	6 (14)	8 (9)	4 (9)
Diarrhoea	26 (29)	4 (9)	6 (7)	5 (12)
Abdominal pain	22 (24)	4 (9)	5 (5)	5 (12)
Nausea	19 (21)	5 (12)	0 (0)	2 (5)
Headache	17 (19)	10 (23)	8 (9)	1 (2)
Vomiting	10 (11)	2 (5)	1 (1)	2 (5)
Cough	7 (8)	7 (16)	4 (4)	0 (0)
Pruritus	7 (8)	3 (7)	2 (2)	0 (0)
Proteinuria	7 (8)	1 (2)	3 (3)	2 (5)
Eosinophilia	6 (7)	2 (5)	0 (0)	3 (7)
Back pain	6 (7)	1 (2)	1 (1)	1 (2)
Oropharyngeal pain	5 (5)	4 (9)	3 (3)	2 (5)
SAEs				
Deterioration of psoriasis	3 (3)	3 (7)	1 (1)	0 (0)
Abortion spontaneous	1 (1)	0 (0)	0 (0)	0 (0)
Drug-induced liver injury	1 (1)	0 (0)	0 (0)	0 (0)
Ligament rupture	1 (1)	0 (0)	0 (0)	0 (0)
Meniscus lesion	1 (1)	0 (0)	0 (0)	0 (0)
Nasal septum deviation	1 (1)	0 (0)	0 (0)	0 (0)
Proteinuria	1 (1)	0 (0)	0 (0)	0 (0)
Urobilinogen urine increased	1 (1)	0 (0)	0 (0)	0 (0)
Vomiting	1 (1)	0 (0)	0 (0)	0 (0)
Concussion	0 (0)	0 (0)	1 (1)	0 (0)
Craniocerebral injury	0 (0)	0 (0)	1 (1)	0 (0)
Forearm fracture	0 (0)	0 (0)	1 (1)	0 (0)
Headache	0 (0)	0 (0)	1 (1)	0 (0)
Muscular weakness	0 (0)	0 (0)	1 (1)	0 (0)
Nasopharyngitis	0 (0)	0 (0)	1 (1)	0 (0)
Pain in extremity	0 (0)	0 (0)	1 (1)	0 (0)
Syncope	0 (0)	0 (0)	1 (1)	0 (0)
Abdominal pain upper	0 (0)	0 (0)	0 (0)	1 (2)
Constipation	0 (0)	1 (2)	0 (0)	0 (0)

FAE, fumaric acid esters; SAE, serious adverse event. [a]AEs leading to permanent study drug discontinuation are listed in Table S2 (see Supporting Information). [b]A complete list of all drug-related AEs is available in Table S3 (see Supporting Information).

For adults, the SmPC recommends six tablets of Fumaderm as the maximum daily dose, which represents 1290 mg (6 × 215 mg) FAE or 720 mg DMF and 570 mg EHF salts.[29] For children and adolescents, a weight-adapted maximum daily dose of 480 mg DMF and 380 mg EHF salts was allowed per study protocol, based on the assumption of a lower bodyweight than 70 kg on average in children and adolescents, and also based on experience in adults and off-label use in adolescents. The mean dose of 301 mg DMF per day applied during weeks 5–40 in the FAE/FAE group indicates that the majority received considerably lower dosages. Subgroup analyses implied a tendency towards better outcomes when higher doses were applied, but adequately powered studies are needed for confirmation. Underdosing in this study seems unlikely considering the achieved improvement in the parameters observed. However, a dose-finding study in the paediatric population is warranted in order to evaluate further the benefit–risk ratio in this population and to elucidate whether the present drug dose strengths of Fumaderm Initial and Fumaderm are best for children, or whether an additional (e.g. intermediate) dose strength would be beneficial for this population, as this would enable more nuanced dose titration.

This study may be limited by the high dropout rate, particularly in the placebo group, which may have been informative

(as this was linked to the current disease status and/or present AEs of the corresponding patient) and attrition bias might result. However, we also conducted an analysis assuming that all patients who dropped out were nonresponders (worst-case approach). Furthermore, the use of a placebo-controlled study design and the exclusion of prior systemic antipsoriatic treatment support the conclusion that the observed effects with respect to the outcome parameters may be ascribed to FAE. Additional randomized controlled trials with larger sample sizes and longer follow-up durations are required for further evaluation of the use of FAE in children. Comparative analyses on different treatment options for this patient population are also needed. Nevertheless, the results from the present study confirm observations from a retrospective data collection[34] and support European Union guidelines recommending FAE in the initial systemic treatment of children and adolescents with moderate-to-severe plaque psoriasis.

Acknowledgments

We thank Dr Petra Jöstingmeyer (medunit GmbH, Cologne, Germany), who provided medical writing services. Biogen GmbH provided funding for medical writing support in the development of this article. Open Access funding enabled and organized by ProjektDEAL.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Inclusion and exclusion criteria; sample size; definition of remission, relapse and rebound; case narrative of drug-induced liver injury; and case narrative of severe proteinuria.

Figure S1 Time in remission: Kaplan–Meier plot.

Figure S2 Time to relapse: Kaplan–Meier plot.

Table S1 PASI 50, PASI 75 and PASI 90 responder rates over time.

Table S2 Adverse events leading to permanent study drug discontinuation.

Table S3 Complete list of drug-related adverse events.

Powerpoint S1 Journal Club Slide Set.