

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/169655>

Please be advised that this information was generated on 2019-11-19 and may be subject to change.

Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: a randomized, double-blind, Fumaderm[®]- and placebo-controlled trial (BRIDGE)*

U. Mrowietz,¹ J.C. Szepletowski,² R. Loewe,³ P. van de Kerkhof,⁴ R. Lamarca,⁵ W.G. Ocker,⁶ V.M. Tebbs⁶ and I. Pau-Charles⁵

¹Psoriasis Center at the Department of Dermatology, University Medical Center Schleswig-Holstein, Campus Kiel, Schittenhelmstraße 7, 24105, Kiel, Germany

²Department of Dermatology, Venereology and Allergology, Wrocław Medical University, Wrocław, Poland

³Department of Dermatology, Medical University of Vienna, Vienna, Austria

⁴Department of Dermatology, Radboud University Medical Center, Nijmegen, the Netherlands

⁵Almirall S.A., Barcelona, Spain

⁶Almirall Hermal, Reinbek, Germany

Linked Comment: Balak. *Br J Dermatol* 2017; **176**:563–564.

Summary

Correspondence

Ulrich Mrowietz.

E-mail: umrowietz@dermatology.uni-kiel.de

Accepted for publication

9 August 2016

Funding sources

This research was funded by Almirall S.A.

Conflicts of interest

U.M. has been an advisor and/or received speaker honoraria and/or received grants and/or participated in clinical trials for the following companies: Abbott/AbbVie, Almirall Hermal, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Foamix, Forward Pharma, Galderma, Janssen, LEO Pharma, Lilly, Medac, Miltenyi Biotec, MSD, Novartis, Pfizer, Teva, UCB, VBL and Xenoport. J.C.S. receives advisory board/consulting fees from AbbVie, Biogen, Biogenetica International Laboratories, Egis Pharmaceuticals, Fresenius, LEO Pharma, Lilly, Novartis, Pierre Fabre, Polpharma, Sandoz and Toray Corporation; and receives speaker fees from AbbVie, Actavis, Adamed, Astellas, Berlin-Chemie Menarini, Fresenius, Janssen-Cilag, LEO Pharma, Mitsubishi Tanabe Pharma, Novartis, Pierre Fabre, Takeda and Vichy, and clinical trial funding from AbbVie, Actelion, Almirall, Amgen, GlaxoSmithKline, Janssen-Cilag, Merck, Mitsubishi Tanabe Pharma, Novartis, Regeneron and Takeda. P.V.K. declares consultancy fees from Celgene, Centocor, Almirall, Amgen, Pfizer, Philips, Abbott, Lilly, Galderma, Novartis, Janssen-Cilag, LEO Pharma, Sandoz and Mitsubishi Tanabe Pharma and carries out clinical trials for Basilea, Pfizer, Lilly, Amgen, AbbVie, Philips

Background Fumaric acid esters (FAEs) are recommended in international guidelines for induction and long-term treatment of adults with moderate-to-severe chronic plaque psoriasis. The fixed combination Fumaderm[®] is approved in Germany, with dimethyl fumarate (DMF) being the main active ingredient.

Objectives To assess the efficacy and safety of a new formulation of DMF (LAS41008), compared with placebo and Fumaderm[®], in adults with moderate-to-severe chronic plaque psoriasis.

Methods In this phase III, double-blind, placebo-controlled, noninferiority trial (BRIDGE, NCT01726933, EudraCT 2012-000055-13), patients were randomized to receive LAS41008, Fumaderm[®] or placebo (2 : 2 : 1) for 16 weeks, up-titrating to a maximum daily DMF dose of 720 mg, depending upon individual response. The coprimary end points were the percentage of patients achieving $\geq 75\%$ improvement in Psoriasis Area and Severity Index (PASI 75) and the percentage achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment (PGA) at week 16.

Results In total, 671 patients were randomized and included in the full analysis set ($n = 267$, LAS41008; $n = 273$, Fumaderm[®]; $n = 131$, placebo). At week 16, 37.5% of patients treated with LAS41008 achieved PASI 75, compared with 15.3% receiving placebo (superiority for LAS41008 vs. placebo: $P < 0.001$) and 40.3% receiving Fumaderm[®] (noninferiority for LAS41008 vs. Fumaderm[®]: $P < 0.001$). Overall, 33% of patients treated with LAS41008 were 'clear' or 'almost clear' in the PGA at week 16, compared with 13.0% receiving placebo ($P < 0.0001$; LAS41008 superiority vs. placebo) and 37.4% receiving Fumaderm[®]. Most treatment-related adverse events were classed as 'mild' in severity.

Conclusions LAS41008 (DMF) is effective in the treatment of adults with moderate-to-severe chronic plaque psoriasis.

What's already known about this topic?

- A combination of fumaric acid esters (FAEs), including dimethyl fumarate (DMF), is approved for the treatment of moderate-to-severe psoriasis in Germany, with a positive risk–benefit profile for long-term use.

Lighting, Janssen-Cilag and LEO Pharma. R.L. has been an advisor and/or received speaker honoraria/grants and/or participated in clinical trials for the following companies: Almirall Hermal, Novartis, BMS and Merck. R.L. is an employee of AstraZeneca PLC, Barcelona, Spain, and previously of Almirall S.A., Barcelona, Spain. W.G.O. and I.P.C. are employees of Almirall. V.M.T. is director of Island View Consulting Ltd, previously of Almirall Hermal, Reinbek, Germany.

- Despite being recommended in international treatment guidelines, FAEs are not available in most European countries.

What does this study add?

- This international, randomized, double-blind trial demonstrates the efficacy and safety of LAS41008 (DMF) for the treatment of adults with moderate-to-severe chronic plaque psoriasis.

*Plain language summary available online

DOI 10.1111/bjd.14947

Psoriasis is a chronic, inflammatory, immune-mediated skin condition, with its prevalence varying according to geographical location. It affects approximately 2–4% of adults in Europe,¹ can be associated with important comorbidity, including cardiovascular and metabolic diseases,² and has a significant negative physical and psychosocial impact on quality of life.³

Up to one-third of patients with psoriasis have a moderate-to-severe form of the disease,^{4,5} defined by a European consensus as body surface area (BSA) involvement > 10% or Psoriasis Area and Severity Index (PASI) > 10 and Dermatology Life Quality Index (DLQI) > 10.⁶ Currently available systemic treatments for moderate-to-severe psoriasis include both small molecules and biologics. Responses to systemic therapies vary according to the individual patient and are associated with drug-specific side-effects. Therefore, there is a need for new systemic treatment options that provide a good balance of efficacy and safety, especially in the long term.⁷

Fumaric acid esters (FAEs) were first investigated for the treatment of psoriasis in 1959. Since 1994, a combination of FAEs, including dimethyl fumarate (DMF) together with calcium, magnesium and zinc salts of monoethyl fumarate (MEF) in two different strengths (Fumaderm[®] Initial, Fumaderm[®], Biogen Idec GmbH, Germany), has been approved in Germany, where it has demonstrated a favourable efficacy and safety profile.^{8,9}

Dimethyl fumarate is considered the main active component in the combination,¹⁰ as the MEF salts alone have not been shown to have significant clinical efficacy.¹¹ The precise mode of action of DMF in psoriasis is not fully understood. DMF is a prodrug that is rapidly converted after oral intake to monomethyl fumarate, which, together with a DMF–glutathione adduct, is the most prominent metabolite.¹² FAEs are known to affect several intracellular pathways with antioxidant, anti-inflammatory and immunomodulating effects.¹³ DMF treatment promotes the generation of interleukin-10-producing type II dendritic cells, polarizing the immune response towards a T helper cell 2 phenotype.¹⁴ FAEs also modulate the nuclear factor (erythroid-derived 2)-like 2 transcriptional pathway, which is required for antioxidant activity.¹⁵

Treatment of moderate-to-severe psoriasis with FAEs has been shown to be efficacious and safe in the long term.⁹ European guidelines for the treatment of psoriasis recommend FAEs for both induction and long-term treatment.¹⁶ Although this treatment remains unlicensed in many countries, there is known use of FAEs in several parts of Europe, especially in patients who fail, or are intolerant to, classic systemic therapies.¹⁶

The BRIDGE trial was designed to investigate the efficacy and safety of LAS41008 (DMF) for the treatment of adults with moderate-to-severe chronic plaque psoriasis.

Patients and methods

Trial design

This was a multicentre, randomized, double-blind, three-arm, phase III trial (clinicaltrials.gov NCT01726933; EudraCT 2012-000055-13) conducted in Austria, Germany, the Netherlands and Poland in adults with moderate-to-severe chronic plaque psoriasis. Patients were recruited from January 2013 and randomized to receive either LAS41008 (DMF), Fumaderm[®] (active comparator) or placebo in a randomization schedule of 2 : 2 : 1 for a 16-week treatment phase, with a subsequent off-treatment follow-up of up to 12 months.

Randomization was performed by the investigators using an interactive web-based response system. The randomization sequence was kept concealed from the investigators during the trial. Treatment was uptitrated over the first 9 weeks, with placebo or up to a maximum daily dose of 720 mg DMF in the LAS41008 or Fumaderm[®] groups (Fig. 1, Table 1), as per clinical practice. After week 4, a reduction to the last tolerated dose was permitted in case of intolerability.

Following completion of an initial 16-week treatment period, patients entered a 12-month treatment-free follow-up period to assess safety, rebound and persistence of effect.

Patients

Patients were randomized if they were aged 18 years or older and had a diagnosis of moderate-to-severe, chronic (for

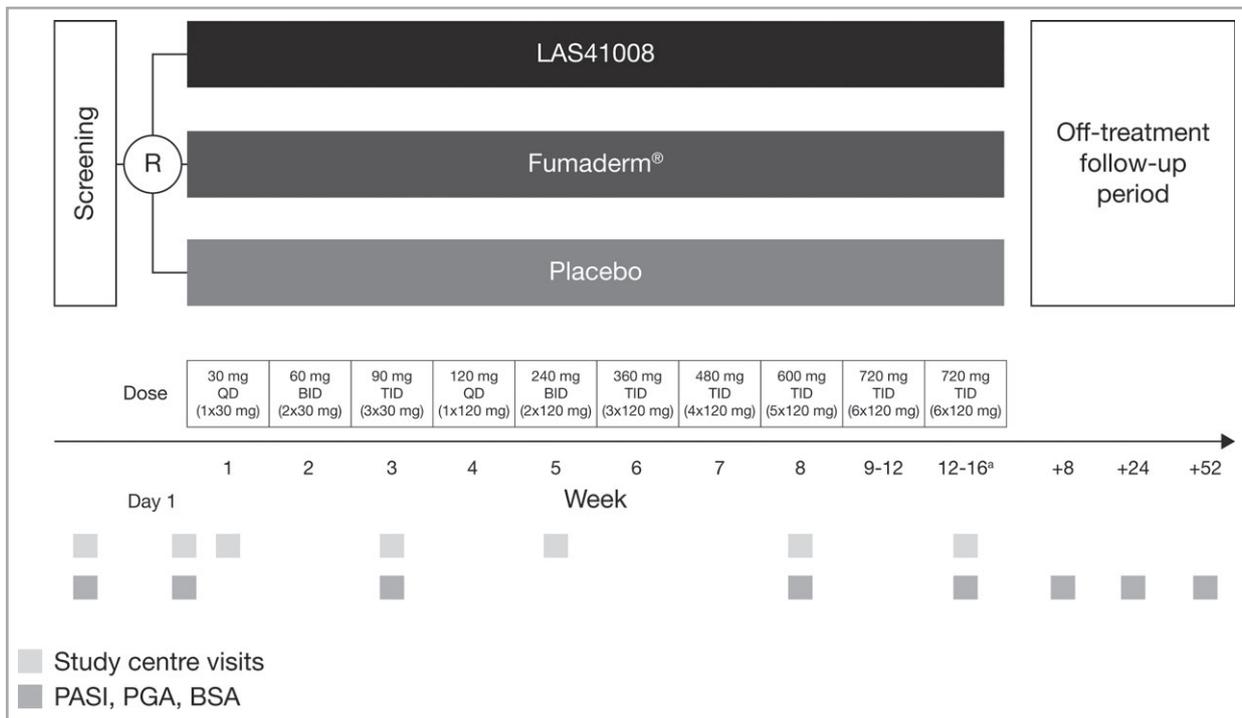


Fig 1. Trial design. BID, twice daily; QD, once daily; R, randomization; TID, three times daily. In the first 3 weeks, 30-mg dimethylfumarate tablets were used, and as the LAS41008 30-mg and Fumaderm® Initial tablets differed in colour and size, a double-dummy technique was used, with each patient also receiving one placebo tablet per tablet of LAS41008 or Fumaderm®. Subsequent uptitration was achieved using indistinguishable 120-mg tablets. ^aTrial-centre visits at weeks 12 and 16; Psoriasis Area and Severity Index (PASI), Physician’s Global Assessment (PGA) and body surface area (BSA) at week 16 only.

Table 1 Dosing schedule of dimethyl fumarate (DMF)

Week	Number of tablets			Daily dose of DMF (mg)
	Morning	Midday	Evening	
30 mg DMF per tablet, double dummy				
1	–	–	1 (+ 1 dummy)	30
2	1 (+ 1 dummy)	–	1 (+ 1 dummy)	60
3	1 (+ 1 dummy)	1 (+ 1 dummy)	1 (+ 1 dummy)	90
120 mg DMF per tablet				
4	–	–	1	120
5	1	–	1	240
6	1	1	1	360
7	1	1	2	480
8	2	1	2	600
9–16	2	2	2	720

≥ 12 months) plaque psoriasis. Moderate to severe was defined as PASI > 10, BSA > 10% and PGA ≥ 3 (i.e. moderate or greater on a scale of 0–5). All previously treated patients underwent a washout period (2 weeks for topical treatments, 1 month for conventional systemic drugs and phototherapy, 3 months for biologics). The use of topical and/or additional systemic treatments was not allowed during the trial. Patients who had previously failed therapy on FAEs due to lack of efficacy or tolerability were excluded, as were patients with baseline leucocyte counts < 3 × 10⁹ cells L⁻¹ and/or lymphocyte

counts < 1 × 10⁹ cells L⁻¹, and pregnant or breastfeeding women.

Assessments

Efficacy was assessed considering the European Medicines Agency’s clinical investigation guidance¹⁷ using the PASI, PGA (six-point scale) and BSA scores, which were measured at screening, baseline, weeks 3, 8 and 16 and each follow-up visit (Fig. 1).

Table 2 Demographic and baseline patient characteristics (treated population)

	LAS41008 (n = 279)	Fumaderm [®] (n = 283)	Placebo (n = 137)
Male, n (%)	174 (62.4)	185 (65.4)	93 (67.9)
Age (years)			
Mean ± SD	44.0 ± 15.2	45.0 ± 13.8	44.0 ± 14.3
Range	18–80	18–87	18–78
Race, n (%)			
White	275 (98.6)	280 (98.9)	137 (100.0)
Black/African American	1 (0.4)	0	0
Asian	1 (0.4)	3 (1.1)	0
Other	2 (0.7)	0	0
PASI total score, mean ± SD	16.3 ± 5.7	16.4 ± 6.79	16.2 ± 4.9
PGA group, n (%) ^a			
Moderate	162 (60.7)	164 (60.1)	79 (60.3)
Moderate to severe	93 (34.8)	94 (34.4)	49 (37.4)
Severe	12 (4.5)	15 (5.5)	3 (2.3)
Body surface area (%), mean ± SD	21.9 ± 11.6	21.3 ± 12.5	21.9 ± 12.3
Prior conventional systemic therapy, n (%)			
Methotrexate	20 (7.2)	39 (13.8)	14 (10.2)
Ciclosporin	12 (4.3)	8 (2.8)	8 (5.8)
Fumaderm [®]	9 (3.2)	11 (3.9)	4 (2.9)
Acitretin	8 (2.9)	15 (5.3)	9 (6.6)
Apremilast	1 (0.4)	1 (0.4)	0
Prior biological therapy, n (%)			
Interleukin inhibitors ^b	7 (2.5)	4 (1.4)	3 (2.2)
TNF- α inhibitors ^c	1 (0.4)	6 (2.1)	0
Prior nondrug therapy including phototherapy, n %	75 (26.9)	86 (30.4)	43 (31.4)

PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; TNF, tumour necrosis factor. ^aThe PGA scale was defined as follows: 0, clear; 1, almost clear; 2, mild; 3, moderate; 4, moderate to severe; 5, severe. ^bIncluding secukinumab, ustekinumab and brodalumab. ^cIncluding adalimumab and etanercept.

End points

The two coprimary efficacy end points were the percentage of patients achieving PASI 75 ($\geq 75\%$ improvement of PASI vs. baseline, considered clinically meaningful)⁶ and the percentage of patients achieving a score of 0 or 1 ('clear' or 'almost clear') in the PGA, both evaluated at week 16 (end of treatment) (Fig. 1).

Secondary end points included PASI 75 at weeks 3 and 8, PASI 50 and PASI 90 at week 16, and scores of 0–1 in the PGA at weeks 3 and 8 and BSA at weeks 3, 8 and 16. Health-related quality of life was measured using the DLQI score, assessed at baseline, week 16 and the 2-month follow-up. Rebound, defined as a worsening of psoriasis over baseline values (PASI $\geq 125\%$), was assessed 2 months after the end of treatment.

Adverse events (AEs), haematology and chemistry laboratory tests, and urinalysis data were collected throughout the treatment period and, if indicated by previous results, potentially up to 12 months in the off-treatment follow-up period.

Statistical analysis

The sample-size calculations were based on PASI 75 response rates of 50% and 10% for LAS41008 and placebo, respectively, and 'clear'/'almost clear' PGA response rates of 40% for LAS41008 and 10% for placebo. For the noninferiority test

of LAS41008 vs. Fumaderm[®] regarding PASI 75 at week 16, a zero difference was assumed and a noninferiority margin of 15% was set. An alpha level of 0.05 was defined and a drop-out rate of 15% was factored into the calculations. A total of 690 patients (276 per active group and 138 in the placebo group) provided a power of $> 99\%$ for the two superiority tests of LAS41008 vs. placebo, and 90% for the noninferiority test of LAS41008 vs. Fumaderm[®].

An interim analysis was planned once data for the two primary efficacy variables were available for 230 patients, to allow sample-size reassessment because of uncertainty in the response-rate assumptions, stopping for futility and identification of safety signals.

All statistical analyses were based on the full analysis set (FAS) and the per protocol set (PPS). As the results of both were consistent, data are presented here only for the FAS. A last-observation-carried-forward approach was used to handle missing data for the PASI- and PGA-derived end points. A sensitivity analysis was conducted for the coprimary efficacy end point, treating missing data as 'nonresponders'. Further details are included in Appendix S1 (see Supporting Information).

The coprimary efficacy end points, PASI 75 and PGA 0–1 at week 16, were analysed using the Wald test for risk differences (differences in responder rates between treatment groups). A hierarchical approach was used to deal with multiple comparisons – first the superiority tests in PASI 75 and

PGA for both the FAS and PPS, and then the noninferiority test for PASI 75 if superiority vs. placebo was demonstrated.

Safety outcomes were summarized descriptively using the safety analysis set.

Results

Overall, 839 patients were screened and 704 were randomized, with 699 receiving at least one dose of trial medication

and included in the safety analysis set (Appendix S1; see Supporting Information) and 671 in the FAS (267, 273 and 131 patients in the LAS41008, Fumaderm[®] and placebo groups, respectively). Patients were recruited from 57 sites throughout Austria, Germany, the Netherlands and Poland. The baseline patient characteristics were well balanced across treatment groups (Table 2). Rates of discontinuations were similar between the LAS41008 and Fumaderm[®] arms (37.1% and 38.5%, respectively), with the most common reasons for

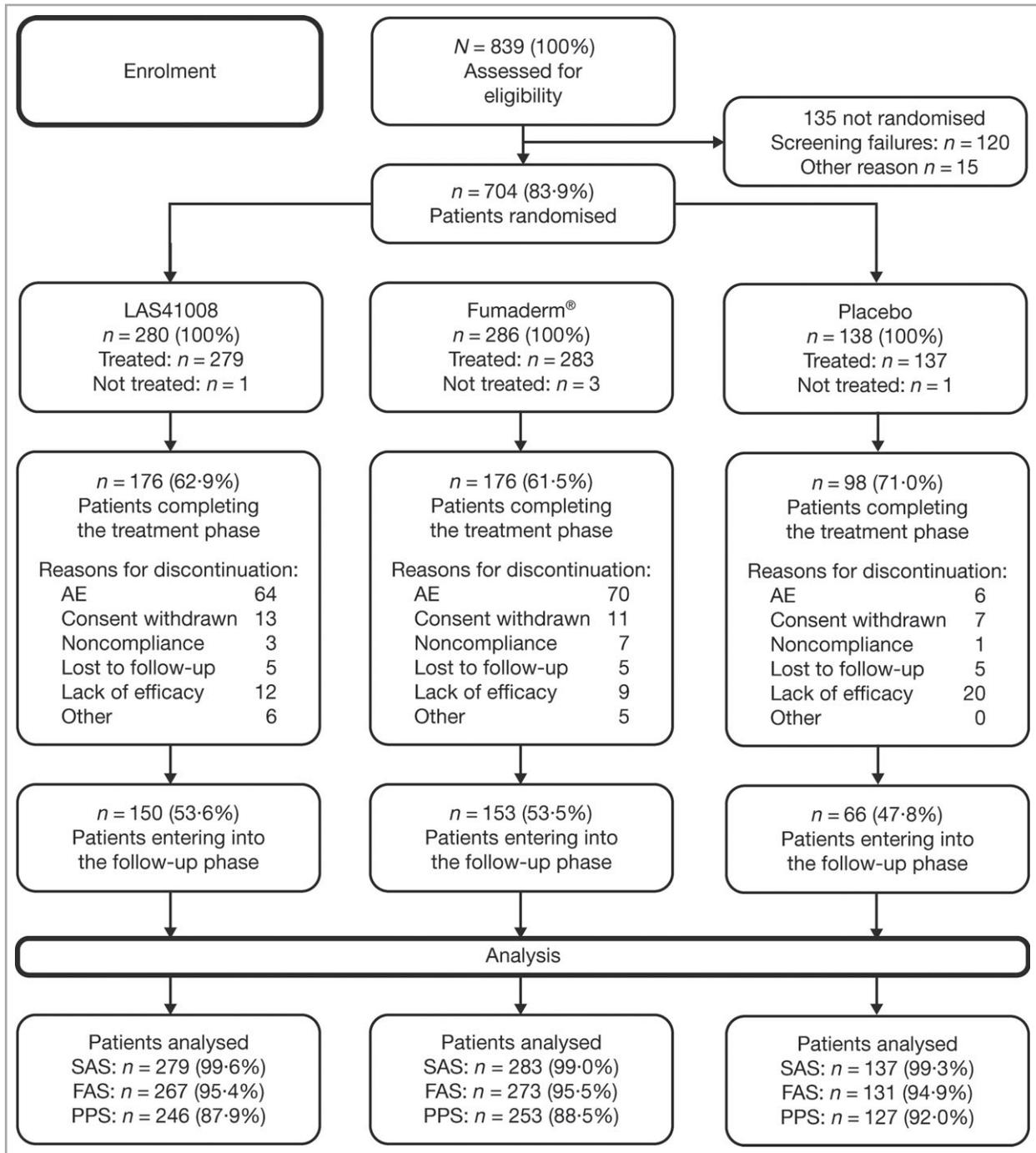


Fig 2. Participant flow. AE, adverse event; FAS, full analysis set; PPS, per protocol set; SAS, safety analysis set.

treatment discontinuation being occurrence of an AE in the LAS41008 (23%) and Fumaderm® arms (24%), and lack of efficacy in the placebo arm (15%) (Fig. 2).

Efficacy

Copriary end points

Significantly more patients achieved PASI 75 at week 16 following treatment with LAS41008 than with placebo [37.5% vs. 15.3%, $P < 0.001$; 99.24% confidence interval (CI) 10.7–33.7%]. Furthermore, LAS41008 was noninferior to Fumaderm® at week 16 (37.5% vs. 40.3%, $P < 0.001$; 99.24% CI -14.0 to 8.4%) (Fig. 3). At week 16, 33.0%, 37.4% and

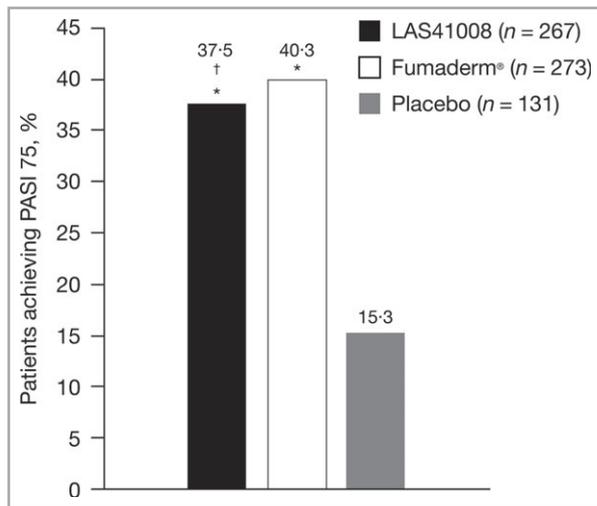


Fig 3. Percentage of patients achieving $\geq 75\%$ improvement in Psoriasis Area and Severity Index (PASI 75) at week 16 (full analysis set). * $P < 0.001$ vs. placebo; [†] $P < 0.001$ noninferiority vs. Fumaderm®.

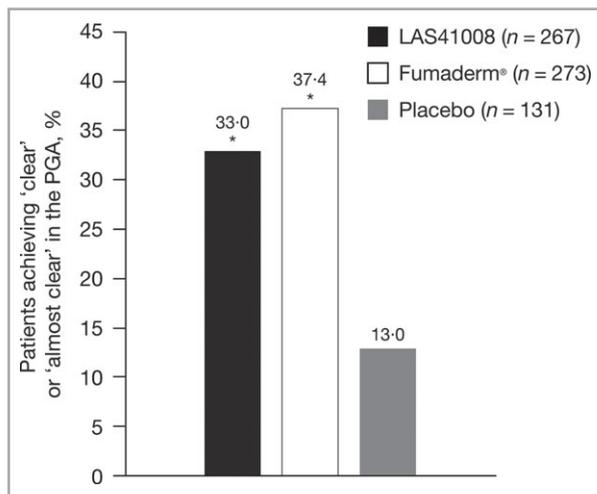


Fig 4. Percentage of patients achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment (PGA) at week 16 (full analysis set). * $P < 0.001$ vs. placebo.

13.0% of patients had achieved a score of 'clear' or 'almost clear' in the PGA in the LAS41008, Fumaderm® and placebo groups, respectively, and LAS41008 was significantly superior to placebo ($P < 0.001$; 99.24% CI 9.0–31.0%) (Fig. 4).

Concomitant intake of potentially nephrotoxic drugs ($n = 108$), such as angiotensin-converting enzyme inhibitors, angiotensin II inhibitors and/or statins, did not have a significant impact on the primary outcome measures or on the safety profile of LAS41008.

Secondary end points

No statistically significant differences between LAS41008 or Fumaderm® and placebo were found in the percentage of patients achieving PASI 75 or PGA 0–1 at weeks 3 or 8 (data not shown).

The percentage of involved BSA decreased from week 3 onwards in the LAS41008 group, with a significant reduction at week 8 compared with placebo ($P = 0.032$; 95% CI -2.93

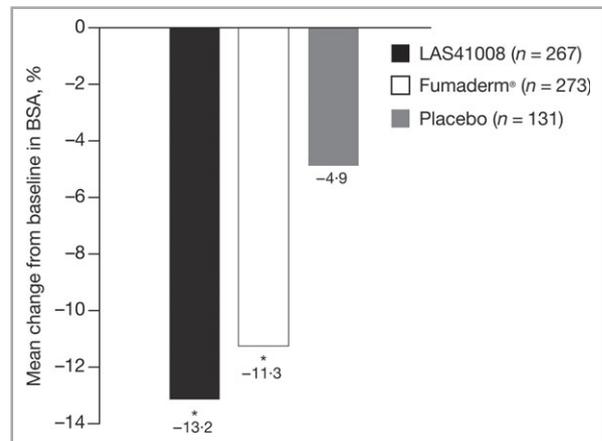


Fig 5. Mean change from baseline in body surface area (BSA) score at week 16 (full analysis set). * $P < 0.001$ vs. placebo.

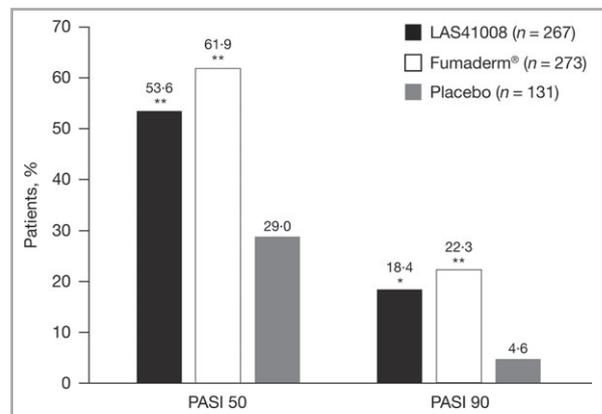


Fig 6. Percentage of patients achieving $\geq 50\%$ improvement in Psoriasis Area and Severity Index (PASI 50) and PASI 90 at week 16 (full analysis set). * $P < 0.001$ vs. placebo; ** $P < 0.0001$ vs. placebo.

to -0.13). By week 16, continuing improvements in BSA were reported, which were statistically significant vs. placebo for both LAS41008 ($P < 0.001$; 95% CI -8.96 to -4.82) and Fumaderm[®] ($P < 0.001$; 95% CI -8.10 to -4.01) (Fig. 5). Results for the PASI, PGA and BSA assessments were consistent between the FAS and PPS (data not shown).

Compared with placebo, significantly more patients receiving LAS41008 achieved PASI 50 at week 16 (53.6% vs. 29.0%, $P < 0.001$; 95% CI 14.7–34.4%). Similarly, LAS41008 was statistically superior to placebo for the percentage of patients achieving PASI 90 at week 16 (18.4% vs. 4.6%, $P < 0.001$; 95% CI 7.9–19.6%) (Fig. 6).

The mean number of tablets taken during the trial did not differ significantly among the active treatment arms (Fig. S1; see Supporting Information).

Rebound at 2 months off treatment

Rebound at 2 months after the end of treatment was recorded in very few patients in the LAS41008 or Fumaderm[®] treatment arms (1.1% and 2.2%, respectively, vs. 9.3% of patients receiving placebo).

Safety

Treatment-emergent AEs (TEAEs) were reported in 83.9% and 84.1% of patients in the LAS41008 and Fumaderm[®] groups, respectively, and in 59.9% of patients in the placebo group. The majority were considered 'mild' in intensity (66.7%, 67.1% and 52.6% in the LAS41008, Fumaderm[®] and placebo groups, respectively). The most frequently reported TEAEs in

Table 3 Adverse events (AEs) reported by $\geq 5\%$ of the patients in any treatment group (safety population)

	LAS41008 (n = 279)	Fumaderm [®] (n = 283)	Placebo (n = 137)
At least one TEAE, n (%)	234 (83.9)	238 (84.1)	82 (59.9)
Preferred term, n (%)			
Diarrhoea	108 (38.7)	113 (39.9)	23 (16.8)
Upper abdominal pain	56 (20.1)	64 (22.6)	11 (8.0)
Abdominal pain	55 (19.7)	45 (15.9)	7 (5.1)
Nausea	30 (10.8)	24 (8.5)	5 (3.6)
Flatulence	15 (5.4)	16 (5.7)	7 (5.1)
Vomiting	13 (4.7)	19 (6.7)	2 (1.5)
Pruritus	24 (8.6)	28 (9.9)	15 (10.9)
Erythema	27 (9.7)	23 (8.1)	3 (2.2)
Skin burning sensation	22 (7.9)	20 (7.1)	3 (2.2)
Nasopharyngitis	18 (6.5)	23 (8.1)	13 (9.5)
Flushing	51 (18.3)	46 (16.3)	2 (1.5)
Lymphopenia	28 (10.0)	30 (10.6)	0
Eosinophilia	25 (9.0)	17 (6.0)	0
Headache	23 (8.2)	23 (8.1)	14 (10.2)

TEAE, treatment-emergent AE.

both the LAS41008 and Fumaderm[®] groups were gastrointestinal disorders (62.7% and 63.3%, respectively), including diarrhoea, abdominal pain, nausea and flatulence. Flushing was also commonly reported (18.3% and 16.3%, respectively) (Table 3).

Lymphopenia was reported in 28 patients (10.0%) in the LAS41008 group, with three patients (1.1%) considered severe ($< 0.5 \times 10^9$ cells L^{-1}), and in 30 (10.6%) patients in the Fumaderm[®] group, with two patients (0.7%) considered severe. Proteinuria was reported in four patients (1.4%) in the LAS41008 group and in six patients (2.1%) in the Fumaderm[®] group. Overall, the frequency and type of the reported TEAEs were very similar and did not differ significantly between the LAS41008 and Fumaderm[®] groups (Table 3).

Twenty-three serious TEAEs were reported in 22 patients (3.2%, 2.8% and 3.6% of patients in the LAS41008, Fumaderm[®] and placebo groups, respectively). Only four of these serious TEAEs, occurring in three patients randomized to Fumaderm[®], were assessed by the investigator as related to treatment (erosive gastritis, gastritis, gastric ulcer and gastro-duodenitis). One death considered unrelated to the medication was reported in a patient receiving Fumaderm[®] (subendocardial ischaemia). No relationship between blood abnormalities and the onset of infections was detected.

Laboratory investigations

At week 16 or upon early treatment discontinuation, the mean total lymphocyte counts had decreased from baseline by 0.52×10^9 cells L^{-1} in both the LAS41008 and Fumaderm[®] groups, and by 0.08×10^9 cells L^{-1} in the placebo group. Similarly, the mean leucocyte counts had decreased from baseline by 0.73×10^9 and 0.69×10^9 cells L^{-1} in the LAS41008 and Fumaderm[®] groups, respectively, compared with 0.04×10^9 cells L^{-1} in the placebo group. Lymphocyte counts below 0.7×10^9 cells L^{-1} were observed during the trial in 22 patients in the LAS41008 group (7.9%), 21 patients in the Fumaderm[®] group (7.4%) and one patient in the placebo group (0.7%). Based on the available follow-up data, white blood cell counts progressively recovered after treatment with either LAS41008 or Fumaderm[®] was stopped.

Serum creatinine values are described in Appendix S1 (see Supporting Information).

Discussion

Fumaric acid esters are a well-established treatment option with a long record of a favourable efficacy and safety profile for adults with moderate-to-severe chronic plaque psoriasis. In Germany, a combination of FAEs is the most frequently prescribed systemic treatment for patients with moderate-to-severe psoriasis. In the Netherlands and Austria, FAEs can be dispensed by pharmacies. Furthermore, FAEs are being used in other European countries such as Ireland,¹⁸ Italy¹⁹ and the U.K.^{20,21}

This randomized, double-blind, placebo-controlled trial has shown that LAS41008 (DMF) is effective for the treatment of psoriasis and can provide an efficacy and safety profile comparable with the equivalent dose of DMF contained in the approved combination of FAEs (Fumaderm®). While LAS41008 (DMF) is not significantly different from Fumaderm® in clinical terms, it may prove easier to access across the European Union, depending on the different national healthcare systems.

International psoriasis guidelines recommend the use of FAEs for the induction and long-term management of the disease.¹⁶ A recent systematic review analysed the data from six randomized active or placebo-controlled trials of FAEs of 12–16 weeks' duration, which included 544 patients with psoriasis.²² Although the end points differed between studies, all studies assessing PASI reported a significant reduction in score from baseline with FAEs compared with placebo. PASI scores were reduced by 71% (vs. 6% with placebo) at week 12 ($P < 0.001$) in one study and 67.8% in another (vs. 10.2% with placebo) at week 16 ($P < 0.001$). A recent systematic review of fumarate use in psoriasis provided similar data.²³

Retrospective data from a German nationwide patient registry do not show an increased risk for the development of infections or malignancies for patients on long-term treatment with FAEs.²⁴

Another meta-analysis that included 16 double-blind, randomized controlled trials of various psoriasis treatments indicated that FAEs appear to be as effective as high-dose etanercept.²⁵ Furthermore, in an open study of 101 patients with severe psoriasis, an improvement in PASI of 80% was reported after 4 months of treatment with FAEs.²⁶ The efficacy of FAEs has also been reported in a number of observational studies,^{9,27} with one reporting similar efficacy to methotrexate²⁸ and another retrospective study showing that 76% of patients achieved PASI 75 at 1 year.²⁹ This is similar to responses reported in a large retrospective trial, where 82% of patients were documented as markedly improved or clear after 36 months of therapy with FAEs, as assessed with the PGA.⁹

The BRIDGE trial has shown that LAS41008 (DMF) is noninferior to the approved combination of FAEs (Fumaderm®), suggesting that DMF is the main active moiety of Fumaderm®, with MEF salts not being essential to achieving a clinically relevant response.

Adverse events were more frequent in the LAS41008 and Fumaderm® groups compared with placebo; however, most were considered 'mild' in severity, mainly comprising gastrointestinal disorders and flushing, which are known side-effects of FAEs.²² Gastrointestinal tolerance can be improved by gradually increasing the dose at treatment initiation, administering the dose with food and temporarily reducing the dose in the case of intolerance.¹⁶ In this trial, the safety profile of LAS41008 (DMF) was very similar to that of Fumaderm®, and no major or unexpected safety concerns were identified.

Lymphopenia is a known potential side-effect of FAEs. In this trial, lymphopenia was reported in 10.0% of patients treated with LAS41008 and in 10.6% of patients treated with

Fumaderm® after 16 weeks. Data from case series suggest that FAE-induced lymphopenia is usually mild, can be managed with dose adjustments, and reverts upon treatment discontinuation.³⁰ The development of severe lymphopenia can increase the risk of rare opportunistic infections. As of November 2015, nine cases of progressive multifocal leucoencephalopathy (PML) have been linked to the use of Fumaderm® for psoriasis since 1994. PML is a rare, progressive, life-threatening, brain-demyelinating disease caused by an opportunistic infection with the JC virus. It has also been described in Patients being treated with Psorinovo® (FAE combination) for psoriasis and with Tecfidera® (DMF) for multiple sclerosis.

There is a direct relationship between low lymphocyte numbers and PML.⁹ To minimize the risk of PML, it is advised not to start treatment with FAEs in patients with abnormal baseline lymphocyte counts, and to monitor lymphocyte counts on a regular basis. It is recommended to reduce the treatment dosage if lymphocyte counts decrease below 0.7×10^9 cells L^{-1} and to stop the treatment dose if lymphocyte counts do not increase a month after dose reduction, or if they fall below 0.5×10^9 cells L^{-1} .^{16,31}

There were limitations to this trial. The primary efficacy end points were measured after only 16 weeks of treatment, of which up to 9 weeks was needed to titrate to the therapeutic dose. This relatively short treatment period may not allow provision of an estimate of the maximum efficacy, considering that the efficacy of FAEs is seen to improve over many months of treatment and continues up to 36 months of treatment.⁹ Discontinuation rates were relatively high, due mainly to the known side-effect profile of FAEs; in this context, the last-observation-carried-forward approach may have diminished the reported treatment effect.

In conclusion, this trial has demonstrated the efficacy and safety of LAS41008 (DMF) for adults with moderate-to-severe chronic plaque psoriasis, showing it to be significantly superior to placebo and noninferior to the approved combination of FAEs (Fumaderm®). The safety profile of LAS41008 was very similar to that of Fumaderm®, and no unexpected safety issues were detected. Once approved, LAS41008 (DMF) will represent a promising new oral treatment option for patients with moderate-to-severe psoriasis across Europe.

Acknowledgments

The authors would like to acknowledge both the patients and physicians without whom this BRIDGE trial would not have been possible. A full list of trial investigators is included in Appendix S1 (see Supporting Information). The authors meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors. They take full responsibility for the scope, direction and content of the manuscript and editorial decisions relating to it, and were involved at all stages of development and have approved the submitted manuscript. The authors received no compensation related to the development of the manuscript. Medical writing

assistance was provided by Laura George, PhD, on behalf of Complete HealthVizion, and was contracted and compensated by Almirall S.A., Spain.

References

- Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol* 2013; **133**:377–85.
- Benson MM, Frishman WH. The heartbreak of psoriasis: a review of cardiovascular risk in patients with psoriasis. *Cardiol Rev* 2015; **23**:312–16.
- Augustin M, Radtke MA. Quality of life in psoriasis patients. *Expert Rev Pharmacoecon Outcomes Res* 2014; **14**:559–68.
- Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003–2004. *J Am Acad Dermatol* 2009; **60**:218–24.
- Neimann AL, Porter SB, Gelfand JM. The epidemiology of psoriasis. *Expert Rev Dermatol* 2006; **1**:63–75.
- Mrowietz U, Kragballe K, Reich K *et al.* Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res* 2011; **303**:1–10.
- Lebwohl MG, Bachelez H, Barker J *et al.* Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. *J Am Acad Dermatol* 2014; **70**:871–81.
- Mrowietz U, Altmeyer P, Bieber T *et al.* Treatment of psoriasis with fumaric acid esters (Fumaderm). *J Dtsch Dermatol Ges* 2007; **5**:716–17.
- Reich K, Thaçi D, Mrowietz U *et al.* Efficacy and safety of fumaric acid esters in the long-term treatment of psoriasis – a retrospective study (FUTURE). *J Dtsch Dermatol Ges* 2009; **7**:603–10.
- Rostami-Yazdi M, Mrowietz U. Fumaric acid esters. *Clin Dermatol* 2008; **26**:522–6.
- Nieboer C, de Hoop D, van Loenen AC *et al.* Systemic therapy with fumaric acid derivatives: new possibilities in the treatment of psoriasis. *J Am Acad Dermatol* 1989; **20**:601–8.
- Rostami-Yazdi M, Clement B, Schmidt TJ *et al.* Detection of metabolites of fumaric acid esters in human urine: implications for their mode of action. *J Invest Dermatol* 2009; **129**:231–4.
- Mrowietz U, Asadullah K. Dimethylfumarate for psoriasis: more than a dietary curiosity. *Trends Mol Med* 2005; **11**:43–8.
- Ghoreschi K, Brück J, Kellerer C *et al.* Fumarates improve psoriasis and multiple sclerosis by inducing type II dendritic cells. *J Exp Med* 2011; **208**:2291–303.
- Brennan MS, Matos MF, Li B *et al.* Dimethyl fumarate and monoethyl fumarate exhibit differential effects on KEAP1, NRF2 activation, and glutathione depletion in vitro. *PLoS ONE* 2015; **10**:e0120254.
- Nast A, Gisondi P, Ormerod AD *et al.* European S3-guidelines on the systemic treatment of psoriasis vulgaris – update 2015 – short version – EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol Venereol* 2015; **29**:2277–94.
- European Medicines Agency. Clinical efficacy and safety: dermatologicals. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000398.jsp&mid=WC0b01ac0580034cf0 (last accessed 12 September 2016).
- Heelan K, Markham T. Fumaric acid esters as a suitable first-line treatment for severe psoriasis: an Irish experience. *Clin Exp Dermatol* 2012; **37**:793–5.
- Carboni I, De Felice C, De Simoni I *et al.* Fumaric acid esters in the treatment of psoriasis: an Italian experience. *J Dermatolog Treat* 2004; **15**:23–6.
- Balasubramaniam P, Stevenson O, Berth-Jones J. Fumaric acid esters in severe psoriasis, including experience of use in combination with other systemic modalities. *Br J Dermatol* 2004; **150**:741–6.
- Burden-Teh E, Lam M, Cohen S. Fumaric acid esters to treat psoriasis: experience in a U.K. teaching hospital. *J Am Acad Dermatol* 2013; **68** (Suppl. 1):AB52.
- Atwan A, Ingram JR, Abbott R *et al.* Oral fumaric acid esters for psoriasis. *Cochrane Database Syst Rev* 2015; **8**:CD010497.
- Balak DM, Fallah Arani S, Hajdarbegovic E *et al.* Efficacy, effectiveness, and safety of fumaric acid esters in the treatment of psoriasis: a systematic review of randomized and observational studies. *Br J Dermatol* 2016; **175**:250–62.
- Reich K, Mrowietz U, Radtke MA *et al.* Drug safety of systemic treatments for psoriasis: results from The German Psoriasis Registry PsoBest. *Arch Dermatol Res* 2015; **307**:875–83.
- Schmitt J, Zhang Z, Wozel G *et al.* Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. *Br J Dermatol* 2008; **159**:513–26.
- Mrowietz U, Christophers E, Altmeyer P. Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study. German Multicentre Study. *Br J Dermatol* 1998; **138**:456–60.
- Balak DMW. Fumaric acid esters in the management of psoriasis. *Psoriasis Targets Ther* 2015; **5**:9–23.
- Inzinger M, Weger W, Heschl B *et al.* Methotrexate vs. fumaric acid esters in moderate-to-severe chronic plaque psoriasis: data registry report on the efficacy under daily life conditions. *J Eur Acad Dermatol Venereol* 2013; **27**:861–6.
- Zweegers J, Otero ME, van den Reek JM *et al.* Effectiveness of biologic and conventional systemic therapies in adults with chronic plaque psoriasis in daily practice: a systematic review. *Acta Derm Venereol* 2016; **96**:453–8.
- Hoefnagel JJ, Thio HB, Willemze R, Bouwes Bavinck JN. Long-term safety aspects of systemic therapy with fumaric acid esters in severe psoriasis. *Br J Dermatol* 2003; **149**:363–9.
- European Medicines Agency. Updated recommendations to minimize the risk of the rare brain infection PML with Tecfidera. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/10/news_detail_002423.jsp&mid=WC0b01ac058004d5c1 (last accessed 12 September 2016).

Supporting Information

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

Appendix S1. Supplementary methods and results.

Fig S1. Mean number of tablets per day for each week of treatment (safety population).