Tepilamide Fumarate (PPC-06) Extended Release Tablets in Patients with Moderate-to-Severe Plaque Psoriasis: Safety and Efficacy Results from the Randomized, Double-blind, Placebo-controlled AFFIRM Study

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OBJECTIVE: Safe, effective, long-term oral therapies are needed for plaque psoriasis. This study aimed to assess the safety and effectiveness of tepilamide fumarate (a fumaric acid ester) extended-release tablets. **METHODS:** This Phase IIb, randomized, double-blind, placebo-controlled, 24-week, multicenter study treated adults with moderate-to-severe plaque psoriasis with tepilamide fumarate 400 mg once (QD) or twice daily (BID), 600 mg BID, or placebo. Coprimary endpoints were the proportion of patients achieving ≥75% reduction in the Psoriasis Area and Severity Index (PASI-75) and Investigator's Global Assessment (IGA) of clear or almost clear (≥2 points' reduction). **RESULTS:** A total of 426 patients were randomized (mean age 49.6 [±13.0] years). There was a ≥75% PASI reduction in 39.7%, 47.2%, 44.3%, and 20.0% in the 400 mg QD, 400 mg BID, 600 mg BID, and placebo groups, respectively; IGA treatment success was 35.7%, 41.4%, 44.4%, and 22.0%, respectively. Between 50%-66% of tepilamide fumarate and 48% of placebo patients experienced ≥1 treatment-emergent adverse event. Gastrointestinal intolerance (20%-42%), infection (6%-18%), and decreased lymphocyte count (4%-9%) were more common with tepilamide fumarate. **LIMITATIONS:** High placebo response somewhat limits the utility of these findings. **CONCLUSIONS:** Patients with moderate-to-severe plaque psoriasis treated with oral tepilamide fumarate demonstrated positive response. **KEY WORDS:** Body surface area (BSA) dermatology, Dermatology Life Quality Index (DLQI), dimethyl fumarate, fumaric acid esters, gastrointestinal, immunomodulating, inflammatory cytokine, Investigator's Global Assessment (IGA), monomethyl fumarate, Nail Psoriasis Severity Index (NAPSI), non-biologic, oral, plaque psoriasis, PPC-06, prodrug, psoriasis, Psoriasis Area and Severity Index (PASI), Psoriasis Scalp Severity Index (PSSI), systemic, tepilamide fumarate, XP23829

Psoriasis is a chronic T-cell mediated autoimmune skin disease affecting 3.2 percent of the U.S. population.[1,2] Treatment aims to reduce disease burden and improve signs and symptoms.[1,3] According to the American Academy of Dermatology, topical therapies (with or without phototherapy) may be insufficient for patients with moderate-to-severe disease, and systemic therapy, including nonbiologics and biologics, may be necessary.[1] Over time, however, the use of the nonbiologic agents (acitretin, cyclosporine, and methotrexate) can lead to target organ toxicity and drug interactions.[3] Treatment with apremilast, a phosphodiesterase [4] (PDE4) inhibitor, is associated with an approximate 15 percent risk of upper respiratory tract infection (URTI).[4] Long-term safety complications associated with biologic therapies (tumor necrosis factor-[TNF]α antagonists, interleukin [IL]-12/23, and IL-17 monoclonal antibody inhibitors) include immunosuppression and the potential for infection, opportunistic disease, or malignancy.[1,3]

Drugs in the fumaric acid esters (FAE) class frequently contain the primary active ingredient dimethyl fumarate (DMF); this oral pro-drug generates the active metabolite monomethyl fumarate (MMF),[5] which has immunomodulatory and neuroprotective effects in cell-based systems.[6,7] Due to its clinical efficacy,[8-12] a fixed-dose combination of DMF and MMF salts (Fumaderm®) has been a first-line systemic treatment for moderate-to-severe psoriasis in Germany for decades.[7,13] This formulation and other DMF's are fairly well-tolerated,[9,11,14] but associated with high rates of gastrointestinal (GI) side effects and flushing over both short- and long-

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TABLE 1. Summary of Patient Baseline Characteristics

CHARACTERISTIC	TEPILAMIDE FUMARATE			PLACEBO (N=102)	TOTAL (N=406)
	400mg QD (N=101)	400mg BID (N=102)	600mg BID (N=101)		
Age, years	48.0 (13.2)	51.0 (12.3)	50.2 (13.7)	49.3 (12.6)	49.6 (12.7)
Male, n (%)	64 (63)	62 (61)	61 (60)	60 (59)	247 (61)
Race, n (%)					
White	93 (93)	91 (89)	87 (86)	92 (90)	363 (90)
Black/AfricanAmerican	6 (6)	4 (4)	10 (10)	5 (5)	25 (6)
Asian	1 (1)	3 (3)	2 (2)	1 (1)	7 (2)
American Indian, Alaska Native	0 (0)	2 (2)	0 (0)	1 (1)	3 (1)
Native Hawaiian, Pacific Islander	0 (0)	1 (1)	0 (0)	0 (0)	1 (< 1)
Other	0 (0)	1 (1)	2 (2)	3 (3)	6 (1)
Ethnicity, n (%)					
Hispanic/Latino	62 (61)	61 (60)	60 (59)	55 (54)	238 (59)
Not Hispanic/Latino	39 (39)	41 (40)	41 (41)	47 (46)	168 (41)
Body mass index, kg/m^2	30.4 (5.0)	30.2 (4.7)	30.7 (4.7)	30.3 (5.0)	30.4 (4.8)
Baseline Psoriasis Area and Severity Index	18.4 (6.4)	18.6 (8.0)	18.0 (6.7)	17.3 (6.2)	18.1 (6.8)
Baseline body surface area affected, %	26 (15)	25 (15)	25 (14)	24 (13)	25 (14)
Baseline Investigator's Global Assessment, n (%)					
3–Moderate	75 (74)	77 (75)	71 (70)	73 (72)	296 (73)
4–Severe	26 (26)	25 (25)	30 (30)	29 (28)	110 (27)
Prior conventional systemic therapy†, n (%)	64 (63)	70 (69)	67 (66)	64 (63)	265 (65)
Prior biologic therapy, n (%)	24 (24)	20 (20)	21 (21)	23 (23)	88 (22)

BID=twice daily; QD=once daily; SD=standard deviation.
* Data are presented as mean (SD) unless otherwise noted.
† Patients who received phototherapy, systemic psoriasis medical therapy, or a combination.

term follow-up.[9,12,15,16]

Lymphopenia (sometimes severe), reversible leucopenia, and transient eosinophilia are also common. In rare cases, progressive multifocal leukoencephalopathy (PML) has occurred; however, periodic blood lymphocyte count monitoring and clear treatment discontinuation criteria can mitigate this complication.[16,17]

Oral treatment options are limited for patients with psoriasis.[3] Tepilamide fumarate (PPC-06), a MMF pro-drug, is a patented extended release tablet formulation absorbed throughout the GI tract and rapidly hydrolyzed to release the active moiety MMF.[6,7] Unpublished Phase I data suggest that PPC-06 provides more efficient and sustained MMF exposure than marketed DMF formulations.[6] This study assessed the safety and efficacy of tepilamide fumarate in patients with moderate-to-severe plaque psoriasis.

METHODS

Participants. This 24-week, Phase IIb, randomized, double-blind, placebo-controlled study was conducted at 74 sites in the United States, primarily dermatology research clinics. Eligible patients were males and non-pregnant females aged ≥18 years with stable, moderate-to-severe plaque psoriasis diagnosed for ≥6 months. Patients were required to be candidates for phototherapy and/or systemic therapy, with no morphology changes or significant disease flares in 6 months. Disease severity had to meet the following criteria: Psoriasis Area and Severity Index (PASI) score ≥12; total body surface area (BSA) ≥10% affected by plaque psoriasis; and Investigator's Global Assessment (IGA) score ≥3. Patients needed to avoid excessive sun exposure/tanning during the study.

Patients were excluded if they had failed ≥3 systemic therapies or received additional psoriasis treatments within prespecified washout or time periods. Study treatment was permanently discontinued if lymphocytes were <500/mm^3 at any visit or <800/mm^3 on 3 consecutive visits. Additional inclusion, exclusion, and discontinuation criteria are available in the Supplemental Appendix. All supplemental materials for this article are available on the online version on jcadonline.com.

This clinical trial was registered on February 5, 2018 (NCT03421197, clinicaltrials.gov) and performed in compliance with International Council for Harmonisation Good Clinical Practices, as well as the ethical principles of the Declaration of Helsinki. All patients provided written informed consent.

Randomization. After a 4-week screening, patients were allocated 1:1:1:1 to tepilamide fumarate 400mg once daily (QD; evening); tepilamide fumarate 400 mg twice daily (BID; morning and evening), tepilamide fumarate 600mg BID; or placebo BID. Random allocation sequencing was generated by Medidata Solutions (Iselin, NJ), and patients were stratified by prior biologic use (a maximum of 30% of patients with prior, washed-out biologic use were permitted to enroll). The investigator and all study representatives were blinded to treatment assignments. After randomization, treatment continued for 24 weeks; this included an initial 5-week dose titration period (Supplemental Figure 1).

Endpoints. Coprimary efficacy endpoints, evaluated at the end of Week 24, included the proportion of patients with a ≥75% reduction from baseline in PASI score (PASI-75) and the proportion who achieved an IGA score of clear or almost clear (0 or 1; i.e., a ≥2-point reduction).

Secondary endpoints included mean absolute change from baseline and proportion of patients achieving: ≥50% and ≥90% reductions in total PASI score (PASI-50 and PASI-90); ≥50% reduction in target fingernail Nail Psoriasis Severity Index score (NAPSI-50); ≥75% reduction in Psoriasis Scalp Severity Index score (PSSI-75); a ≥5-point decrease in Dermatology Life Quality Index (DLQI) score in patients with a baseline score ≥5; and BSA percentage reductions. The NAPSI is a numeric, objective tool used to evaluate nail psoriasis.[18] The PSSI is scalp-specific modification of the PASI.[19] The DLQI is a validated 10-item questionnaire measuring the impact of skin conditions on daily activities.[20]

Patients returned at Week 25 for safety

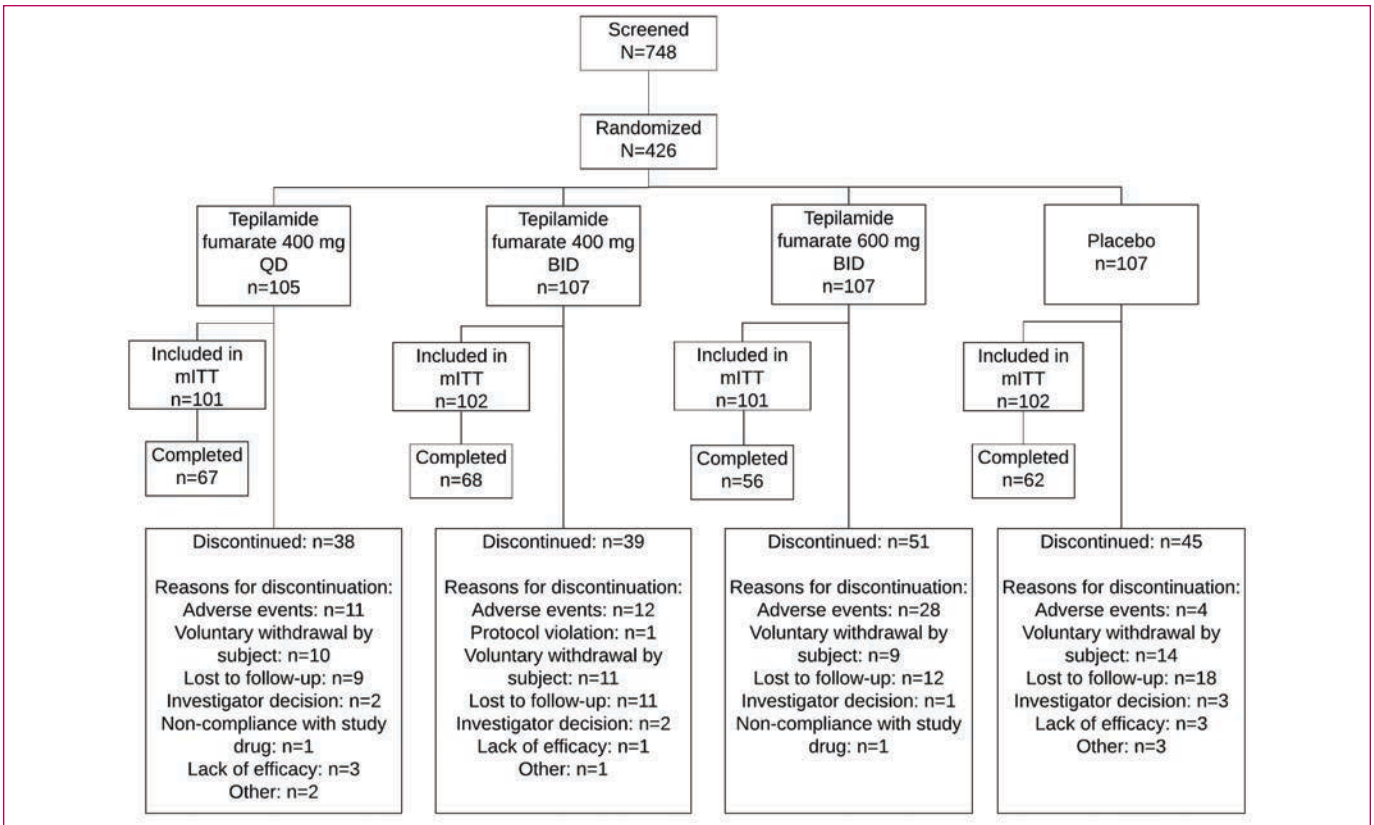

FIGURE 1. Disposition of study participants; mITT: modified intent-to-treat

follow-up, with safety assessed through AE monitoring, clinical laboratory tests, vital signs, physical examinations, pregnancy testing, and electrocardiograms. Supplemental Table 1 summarizes the assessment schedule.

Statistical methods. A sample of 400 was estimated to yield ≥84% power to test the coprimary efficacy endpoints. Each dichotomized coprimary endpoint was analyzed using a logistic regression model adjusted for treatment group, baseline body mass index, and pooled analysis center. Multiple imputation was used to address missing data for the primary efficacy analysis. Modified non-responder imputation (m-NRI) and last observation carried forward (LOCF) were also analyzed and used as sensitivity analyses to assess the robustness of efficacy findings. Each tepilamide fumarate dose was compared to placebo. Hypothesis testing for all dose groups was conducted sequentially using a 2-sided type I error rate of 0.05; PASI and IGA response rates were rejected at the 0.05 significance level.

The modified intent-to-treat (mITT) population was used for the primary efficacy analysis and included all randomized patients with ≥1 treatment dose and ≥1 post-dose efficacy assessment. The safety population included all patients who received ≥1 treatment dose. All analyses were performed using SAS (Version 9.4).

RESULTS

A total of 426 patients were randomized, 406 were included in the mITT population (tepilamide fumarate 400 mg QD [n=101]; 400 mg BID [n=102]; 600 mg BID [n=101]; placebo BID [n=102]), and 253 (59%) completed the study (Figure 1). Most were male (n=247/61%) and white (n=363/90%), with a mean age of 49.6 (±13.0) years (Table 1). At baseline, mean (SD) PASI was 18.1 (6.8); 73% and 27% of patients had an IGA score of 3 (moderate) or 4 (severe), respectively; mean (SD) BSA involvement was 25% (14%); and 88 (22%) patients had received prior biologic therapy.

At Week 24, all treatment groups showed higher PASI-75 response and IGA treatment success rates (Table 2, Supplemental Figures 2–3). PASI-75 response rates and odds ratios (OR, 95% CI) were 39.7% (3.1 [1.5-6.8]), 47.2% (3.6 [1.6-8.2]), and 44.3% (3.2 [1.5-7.0]), respectively, with tepilamide fumarate 400 mg QD, 400 mg BID, and 600 mg BID, versus 20.0% ($P<0.05$, all comparisons) with placebo. PASI-75 response was not significantly different between treatment groups. IGA treatment success rates and ORs (95% CI) were 35.7%, (2.2 [1.0-4.6]), 41.4% (2.6 [1.2-5.8]), and 44.4% (2.9 [1.3-6.5]), respectively, with tepilamide fumarate 400 mg QD, 400 mg BID, and 600 mg BID, versus 22.0% ($P<0.05$, all comparisons) with placebo. IGA treatment success was not significantly different between treatment groups. Similar PASI-75 and IGA success rates were observed with alternative imputations and in case analyses.

All treatment groups showed a gradual, progressive improvement in mean total PASI scores and PASI-50 and PASI-90 response rates from baseline to Week 24 (Table 3).

Mean PASI improvement over baseline at Week 24 ranged from 58.6%-65.5% with tepilamide fumarate (10.7-12.0-point reduction) versus 37.9% with placebo (6.7-point reduction) ($P\leq0.001$, all doses). At Week 24, PASI-50 and PASI-90 response rates ranged from 68.8%-75.0% and 17.3%-20.9% with tepilamide fumarate, respectively, versus 40.8% ($P<0.001$,

TABLE 2. Analysis of Coprimary Efficacy Outcomes At Week 24

MODIFIED INTENT-TO-TREAT POPULATION	TEPILAMIDE FUMARATE			PLACEBO (N=102)
	400mg QD (N=101)	400mg BID (N=102)	600mg BID (N=101)	
PASI-75				
MI	39.7%	47.2%	44.3%	20.0%
OR (95% CI)*	3.1 (1.5-6.8) *P*=0.004	3.6 (1.6-8.2) *P*=0.002	3.2 (1.5-7.0) *P*=0.004	
LOCF	34.4% *P*=0.003	39.0% *P*=0.003	36.0% *P*=0.011	17.0%
m-NRI	44.3% *P*=0.008	50.7% *P*=0.005	51.7% *P*=0.010	24.2%
OC	46.3% *P*=0.008	51.5% *P*=0.009	52.5% *P*=0.014	25.4%
IGA IMPROVEMENT				
MI	35.7%	41.4%	44.4%	22.0%
OR (95% CI)*	2.2 (1.0-4.6) *P*=0.044	2.6 (1.2-5.8) *P*=0.021	2.9 (1.3-6.5) *P*=0.010	
LOCF	26.5% *P*=0.024	31.0% *P*=0.009	31.0% *P*=0.011	14.0%
m-NRI	37.1% *P*=0.029	42.0% *P*=0.012	43.3% *P*=0.014	19.7%
OC	38.8% *P*=0.026	42.6% *P*=0.018	44.1% *P*=0.018	20.6%
Per protocol population	n=62	n=60	n=57	n=56
PASI-75, m-NRI	46.8% *P*=0.002	50.0% *P*=0.012	52.6% *P*=0.009	23.2%
IGA improvement, m-NRI	38.7% *P*=0.027	41.7% *P*=0.027	43.9% *P*=0.023	19.6%

BID=twice daily; CI=confidence interval; IGA=Investigator's Global Assessment; LOCF=last observation carried forward; MI=multiple imputation; m-NRI=modified-nonresponder imputation; OC=observed cases; OR=odds ratio; PASI=Psoriasis Area and Severity Index; QD=once daily.

all doses) and 5.5% ($P<0.05$, all doses) with placebo (Table 3, Supplemental Figures 4–5).

A greater proportion of patients receiving tepilamide fumarate achieved fingernail NAPSI-50, PSSI-75, DLQI, and BSA response. At Week 24, NAPSI-50, PSSI-75, and DLQI, rates ranged from 34.8%–50.0%, 38.9%–53.8%, and 63.1%–70.1% with tepilamide fumarate, respectively, versus 19.4%, 26.1%, and 45.3% with placebo (Table 3, Supplemental Figures 6–8). Mean percent change in BSA at Week 24 ranged from -40.3% to -48.7% in patients treated with tepilamide fumarate versus -27.2% change with placebo.

Safety results. The following number of patients experienced ≥1 treatment-emergent adverse event (TEAE) of any severity: 400 mg QD (53 [50.5%]); 400 mg BID (56 [52.3%]); 600 mg BID (70 [66.0%]); and placebo (51 [47.7%]). Among tepilamide fumarate-treated patients, the most frequently reported TEAEs were due to diarrhea (7%-23%), nausea (7%-10%), abdominal pain (8%-20%), lymphopenia (4%-9%), decreased lymphocyte count (4%-8%), and eosinophilia/increased eosinophil count (5%-6%) (Supplemental Table 2).

Treatment-related TEAEs were higher with tepilamide fumarate 600 mg BID (146 events in 53 [50.0%] patients) and 400 mg BID (113 events in 49 [45.8%] patients) than in the 400 mg QD (84 events in 34 [32.4%] patients) and placebo groups (27 events in 17 [15.9%] patients). Eight serious adverse events were reported in 7 patients: 3 events (3 patients) in the 400 mg BID group; 3 events (2 patients) in the 400 mg QD group; and 2 events (2 patients) in the placebo group. Of these, 4 were probably not related to study treatment, 2 were not related, and 2 were possibly related. No deaths were reported.

The number of patients who discontinued the study due to an AE was 10 (9.5%), 12 (11.2%), 29 (27.3%), and 4 (3.7%) in the tepilamide fumarate 400 mg QD, 400 mg BID, 600 mg BID, and placebo groups, respectively. Of these discontinuations, 2 (1.9%), 7 (6.5%), 18 (17.0%), and 1 (0.9%) occurred during the titration period (first 35 days), respectively, while 8 (7.6%), 5 (4.7%), 11 (10.4%), and 3 (2.8%) occurred after (Day 36 through Week 24). The most common AEs leading to discontinuation were diarrhea and abdominal pain. In the tepilamide fumarate and placebo groups, respectively, 1 (1.0%), 5 (4.7%), 10 (9.4%), and 0 patients discontinued due to diarrhea, and 2 (1.9%), 2 (1.9%), 6 (5.7%), and 0 discontinued due to abdominal pain. There were no clinically important changes in vital signs or laboratory results.

A dose-dependent trend towards reduction in mean absolute lymphocyte count was observed with tepilamide fumarate at approximately Week 4 and stabilized around Week 12. Four (3.8%) patients in the tepilamide fumarate 600 mg BID group and 1 (0.9%) in the 400 mg BID group discontinued due to lymphopenia or decreased lymphocyte count (Table 4); lymphopenia reversed with treatment cessation.

DISCUSSION

Over 24 weeks of treatment, tepilamide fumarate showed positive effect in patients with moderate-to-severe plaque psoriasis. Treatment typically took effect within 8-12 weeks and showed progressive benefit. PASI-75 results for the active tepilamide fumarate doses (400 mg QD/400 mg BID/600 mg BID) were 39.7%/47.2%/44.3%, versus 20.0% with placebo, while IGA success rates were 35.7%/41.4%/44.4%, versus 22.0% with placebo. These results are similar to a 2017 randomized, 16-week, double-blind evaluation of two FAEs (DMF and Skilarence® [DMF]), in which 37.5% and 40.3% of patients achieved PASI-75, and 33% were "clear" or "almost clear" using the Physician's Global Assessment (a precursor to the IGA).[12,21]

In the current study, 50%/52%/62% of patients treated with tepilamide fumarate and 48% of placebo patients experienced TEAEs. A similarly high placebo TEAE rate has been observed in randomized trials of other DMF formulations. Patients treated with tepilamide fumarate (in particular 400 mg QD and BID)

had lower TEAE incidence than clinical trials of other DMF formulations (range: 69%-84%). The most common events observed with other DMF formulations were GI intolerance (range, 56%-63%) and abnormal flushing (16%-31%).[9,12,15] In this study, 20%/32%/42% of patients treated with tepilamide fumarate had TEAEs related to GI intolerance and ≤2% experienced flushing. The proportion of tepilamide fumarate patients who discontinued due to AEs was 10%/11%/26%, again lower for 400 mg QD and BID than rates reported in prior DMF trials (24%-31%).[9,12] No events of PML or deaths occurred. Last, compared to prior DMF research,[12] this study showed similar rates of low lymphocyte (7%/11%/15%) and increased eosinophil count (5%/5%/6%).

In general, FAEs offer some safety advantages over other psoriasis therapies. Treatment with certain biologic drugs increases risk for serious infection (such as tuberculosis reactivation). In a 3-year French registry analysis, patients receiving infliximab or adalimumab had an elevated opportunistic infection risk (OR, 17.6 [95% CI, 4.3-72.9] and 10.0 [2.3-44.4], respectively).[22,23] Additionally, antibodies develop in patients receiving biologic therapies, which may reduce treatment efficacy over time.[1,3] Patients treated with tyrosine kinase 2 inhibitors and the PDE4 inhibitor apremilast are at elevated risk for URTI.[4,24,25] Last, methotrexate and ciclosporin are associated with cumulative liver and kidney toxicity, respectively.[3]

No evidence suggests increased risk for systemic infection, tuberculosis reactivation, or organ toxicity with FAEs.[7,17] An evaluation of German registry data (2008-2012) showed that FAEs had the lowest infection rate among all drugs licensed for systemic psoriasis.[26] A recent European consensus document recommends DMF for patients who are candidates for acitretin, ciclosporin, and methotrexate, as well as those previously treated with other systemic agents. This consensus prioritizes DMF treatment before biologics, and in biologics non-responders.[13]

Oral tepilamide fumarate is likely to be better tolerated than available DMF formulations and may be a promising treatment addition for moderate-to-severe plaque psoriasis. Of the 3 doses evaluated, tepilamide fumarate 400 mg BID strikes a balance between efficacy and tolerability and has been selected for further clinical development.

TABLE 3. Analysis of Secondary Endpoints at Week 24, Modified Intent-to-Treat Population

	TEPILAMIDE FUMARATE			PLACEBO (N=102)
	400mg QD (N=101)	400mg BID (N=102)	600mg BID (N=101)	
Total PASI mean absolute change, MI	-10.7	-12.0	-11.7	-6.7
LSM (SE) differences*	-4.6 (1.1) *P*<0.001	-5.3 (1.1) *P*<0.001	-5.4 (1.1) *P*<0.001	0
PASI-50 response, MI	68.8%	75.0%	72.6%	40.8%
OR (95% CI)*	3.6 (1.8-7.5) *P*<0.00001	4.6 (2.1-9.7) *P*<0.00001	4.0 (1.9-8.6) *P*<0.00001	
PASI-90 response, MI	17.3%	20.9%	18.8%	5.5%
OR (95% CI)*	3.7 (1.2-11.1) *P*=0.019	3.9 (1.3-11.8) *P*=0.017	3.4 (1.1-9.8) *P*=0.027	
NAPSI-50 response, n/N (%), LOCF	10/26 (38.5%)	8/23 (34.8%)	12/24 (50.0%)	6/31 (19.4%)
OR (95% CI)*	2.6 (0.8-8.5) *P*=0.118	2.3 (0.7-7.8) *P*=0.197	4.2 (1.3-13.8) *P*=0.020	
PSSI-75 response, n/N (%), MI	33/85 (38.9%)	37/79 (47.7%)	43/81 (53.8%)	20/77 (26.1%)
OR (95% CI)*	1.9 (0.9-4.0) *P*=0.120	2.6 (1.2-5.6) *P*=0.019	3.1 (1.4-7.2) *P*=0.007	
DLQI response, n/N (%), LOCF	38/60 (63.3%)	41/65 (63.1%)	47/67 (70.1%)	29/64 (45.3%)
OR (95% CI)*	2.5 (1.1-5.4) *P*=0.023	2.4 (1.1-5.2) *P*=0.024	3.5 (1.6-7.6) *P*=0.002	
BSA, mean % change	-40.3	-46.3	-48.7	-27.2
LSM (SE) differences*	-14.4 (6.2) *P*=0.020	-18.8 (6.2) *P*=0.003	-21.3 (6.2) *P*<0.001	

BID=twice daily; DLQI=Dermatology Life Quality Index; LSM=least squares mean; MI=multiple imputation; NAPSI=Nail Psoriasis Severity Index=OR, odds ratio; PASI=Psoriasis Area and Severity Index=PSSI, Psoriasis Scalp Score Index; QD=once daily; SE=standard error.
* Treatment versus placebo.

TABLE 4. TEAEs of Low Lymphocyte Count

TEAE, NUMBER OF PATIENTS (%)	PLACEBO	TEPILAMIDE FUMARATE		
		400mg QD	400mg BID	600mg BID
Lymphopenia	0 (0%)	4 (4%)	4 (4%)	10 (9%)
Lymphocyte Count Decreased	1 (1%)	4 (4%)	9 (8%)	6 (6%)
Total*	1 (0.94%)	7 (6.67%)	12 (11.22%)	16 (15.09%)
Discontinuations for TEAEs of low lymphocyte count, number of patients (%)				
Lymphopenia	0 (0%)	0 (0%)	0 (0%)	3 (3%)
Lymphocyte Count Decreased	0 (0%)	0 (0%)	1 (0.94%)	1 (0.94%)
Total	0 (0%)	0 (0%)	1 (0.94%)	4 (3.77%)

*Includes patients in whom 'lymphopenia' or 'lymphocyte count decreased' were reported ≥1 time, or 'lymphopenia' and 'lymphocyte count decreased' were both reported.
BID=twice daily; QD=once daily; TEAE=treatment-emergent adverse event.

Study limitations. Treatment efficacy was not confounded by the use of supplemental therapies; however, a high placebo response was seen after Week 16. There was also a relatively high dropout rate due to AEs (10%-26%), voluntary withdrawals (13%), and loss to follow-up (12%). A 35%-40% dropout rate is common in DMF clinical studies.[9,12] Furthermore, dropouts in this study due to AEs in the 400 mg BID group were highest during the 35-day titration period (n=7) and decreased thereafter (n=5 over 133 days), suggesting tepilamide may be better

tolerated after initial titration.

The long-term efficacy and safety of tepilamide fumarate requires confirmatory research. Since this study focused on patients with plaque psoriasis, results may not be generalizable to individuals with non-plaque psoriasis or excluded comorbidities.

CONCLUSION

Patients with moderate-to-severe plaque psoriasis treated with oral tepilamide fumarate demonstrated positive response and treatment was well-tolerated. The most common AEs were dose-dependent and associated with GI tolerability and decreased lymphocyte count. Oral tepilamide fumarate appears to have similar effectiveness to existing DMF formulations, with lower rates of TEAEs. The clinical development of tepilamide fumarate 400 mg BID may help to address unmet treatment needs in this patient population.

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