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ORIGINAL RESEARCH

Long-Term Treatment with Dimethyl Fumarate for Plaque Psoriasis in Routine Practice: Good Overall Effectiveness and Positive Effect on Impactful Areas

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ABSTRACT

Introduction: Dimethyl fumarate (DMF) is an oral compound to treat plaque psoriasis. Data on the treatment of patients with psoriasis affecting impactful areas are scarce. In this interim analysis of the prospective, noninterventional SKILL study, we summarized results of DMF treatment regarding effectiveness (overall and in impactful areas) and safety.

Methods: Data from 676 patients suffering from moderate-to-severe plaque psoriasis were analyzed after 52 weeks of DMF treatment. Of these, 257 had data available after 52 weeks. The considered impactful areas were nails, palms, soles, and scalp. Data analysis included observed cases (OC) and last observation carried forward (LOCF).

Results: All effectiveness parameters improved after 52 weeks. The Psoriasis Area and Severity Index score was reduced by 79.5% (OC) and 65.7% (LOCF). Compared with baseline, improvements were shown for 70.2% of the patients in their nail psoriasis [nail-Physician Global Assessment (PGA)] and for 57.3% in palmoplantar disease (palmoplantar-PGA). The proportion of patients with scalp-PGA 0/1 (clear/almost clear) increased significantly to 79.8% (OC) and 69.3% (LOCF, both $p < 0.001$) (versus 37.5% and 36.6% at baseline, respectively). Significant reduction of pruritus ($p < 0.001$) was also observed. No unexpected

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adverse drug reactions were observed.
Conclusion: Long-term treatment with DMF in routine practice showed good overall effectiveness and safety, and a positive effect on plaque-psoriasis-affected impactful areas.

Keywords: Dimethyl fumarate; Impactful areas; Nail; Palmoplantar; Psoriasis; Scalp

Key Summary Points
Why carry out this study?
The burden of psoriasis, particularly if impactful areas such as the scalp, nails, palms, and soles are affected, is very high
There were limited data available on dimethyl fumarate (DMF), an approved treatment for moderate-to-severe plaque psoriasis, in patients with psoriasis affecting impactful areas
The objective was to assess the long-term effectiveness and safety of DMF in patients with moderate-to-severe psoriasis, particularly those with involvement of impactful areas
What was learned from the study?
Long-term DMF treatment (until 52 weeks) showed good overall effectiveness and safety in routine practice
A positive effect on plaque-psoriasis-affected impactful areas, such as nails, palmoplantar area, and scalp, was shown as well

INTRODUCTION

A proprietary mixture of fumaric acid esters (FAE) was first licensed in 1994 in Germany for severe psoriasis in adults, and the label was extended in 2008 to moderate psoriasis [1–3]. The metabolite of dimethyl fumarate (DMF), monomethyl fumarate, was later recognized as the active moiety [2, 3]. DMF (Skilarence) has been available in Germany since October 2017 after being approved by the European Medicines Agency. FAE are recommended for initial and long-term treatment of moderate-to-severe chronic plaque psoriasis [4]. In Germany, FAE are the most frequently prescribed first-line systemic agents for psoriasis [5].

The burden of disease, particularly if impactful areas such as the scalp, nails, palms, or soles are affected, is very high [6–8]. Treatment response in these difficult-to-treat areas is often not as good as in other body regions. To date, there are only limited data available on DMF treatment in patients with psoriasis affecting impactful areas. In this prospective, multicenter, noninterventional study (NIS), we assessed the effectiveness and safety of long-term DMF treatment over a period of 52 weeks in patients with moderate-to-severe psoriasis and of those with (co-)involvement of impactful areas.

METHODS

Study Design and Patients

SKILL (**SKIL**arence in **L**ong-term treatment) is a prospective, multicenter, noninterventional study assessing the effectiveness and safety of long-term DMF treatment in patients with moderate-to-severe plaque psoriasis in routine dermatological practice over a total observational period of 2 years per patient. This interim analysis (data cutoff March 2020) included data from a total of 676 patients recruited from 129 German study sites to allow for a representative sample size. After 52 weeks, data from 257 patients were available for our interim analyses. The estimated time between visits, adapted according to routine practice, was approximately 3 months. Patients were asked to participate after the physician's decision for treatment with DMF was made; then, their written informed consent was obtained before patients entered the study. DMF dosing with 30 mg and 120 mg tablets was done according to the recommendations provided in the

summary of product characteristics and at the discretion of the physician.

The study received approval from the ethics committee of the Hamburg Medical Association and was reported to the responsible federal authority, German National Association of Statutory Health Insurance Physicians, Central Federal Association of Health Insurance Funds, and Association of Private Health Insurance e.V. The study was performed in accordance with the 1964 Declaration of Helsinki, and its later amendments. All subjects provided informed consent to participate in the study.

Outcomes

Routine assessments of psoriasis severity included body surface area (BSA), Psoriasis Area and Severity Index (PASI) [9], and five-point Physician Global Assessment (PGA) [10] and, for impactful areas, the PGA per area, i.e., scalp-PGA, nail-PGA and palmoplantar (PP)-PGA. Patients reported Dermatology Life Quality Index [11] and psoriasis-related itch using the itch numerical rating scale (NRS) [12]. Further assessments included baseline characteristics and adverse drug reactions (ADRs) and serious ADRs (SADRs).

Statistical Methods

Statistical analyses were descriptive. Patients who had taken DMF at least once (intention-to-treat population, ITT) were analyzed; the safety population was equivalent to ITT. For variables recorded several times during the course of the study, an analysis of all values present (observed cases, OC) and an analysis according to the last observation carried forward (LOCF) method is provided per timepoint. The latter was applicable if a baseline value and at least one further value after baseline was documented. A Wilcoxon signed-rank test was used for analyzing the change in BSA, absolute PASI, and PASI reduction from baseline to week 52. Psoriasis severity at week 52 versus baseline [PASI < 3 and PASI < 5, scalp-PGA 0/1 (clear/almost clear), nail-PGA 0/1, PP-PGA 0/1, itch NRS < 3 (mild or no pruritus)] was analyzed using the McNemar's test. Data were analyzed with Statistical Analysis System version 9.4, considering a statistical significance (p) of 0.05 for all statistic tests performed.

RESULTS

Patient Population and Baseline Characteristics

In total, 676 patients suffering from moderate-to-severe plaque psoriasis were included. Of these, 38.0% had data available after 52 weeks of treatment, 44.2% discontinued the treatment (defined as occurring within 365 days of treatment initiation), and 17.8% had no data available at week 52 at the time of the cutoff date for the interim analysis (Table 1). The mean age of the total population at baseline was 47.5 ($\pm$ 15.4) years, and 59.6% were males. Overall, at baseline, 30.8% of the patients presented with palmoplantar psoriasis, 78.1% with scalp involvement, and 36.5% with involvement of the nails (i.e., if the respective PGA was mild, moderate, severe, or very severe). Baseline characteristics and severity of patients with data at week 52 were comparable to the total population (Table 1).

Treatment Parameters

The mean daily maintenance dose at week 52 was 294 mg, i.e., approximately 2.5 tablets, and the median was 240 mg, i.e., 2 tablets. With 75% of the patients, the majority received a daily maintenance dose between 120 and 480 mg, and 10% of the patients received a low-dose maintenance therapy of less than 120 mg DMF per day (Fig. 1).

Effectiveness

For the overall study population, the mean BSA improved from baseline to week 52 from 23.6 [95% confidence interval (CI) 22.3–25.0] to 6.2 (95% CI 5.2–7.2, $p < 0.001$) for OC, and from 23.7 (95% CI 22.1–25.3) to 10.2 (95% CI

Table 1 Demographic and baseline characteristics

	All patients			Patients with data at week 52		
	Mean (SD)	%	*N*	Mean (SD)	%	*N*
Patients at baseline	–	100	676	–	–	–
Patients completed week 52 visit	–	38.0	257	–	100	257
Treatment termination	–	44.2	299	–	–	–
No data available for week 52 at the timepoint of interim analysis	–	17.8	120	–	–	–
Age, years	47.5 (15.4)	–	676	47.8 (14.1)	–	257
Males, %	–	59.6	676	–	61.1	257
Body weight, kg	83.9 (17.5)	–	665	82.2 (15.7)	–	253
BMI, kg/m^2						
Total	27.7 (5.2)	–	665	27.4 (4.6)	–	253
Males	27.8 (4.6)	–	395	27.5 (4.2)	–	154
Females	27.6 (6.0)	–	270	27.2 (5.2)	–	99
Disease duration, years	15.2 (13.8)	–	664	15.7 (12.5)	–	253
PASI	14.6 (9.6)	–	663	14.4 (10.1)	–	250
Proportion of patients with PASI > 10	–	65.3	663	–	64.4	250
BSA, %	23.6 (17.8)	–	668	25.1 (18.2)	–	254
Proportion of patients with BSA > 10	–	81.7	668	–	83.1	254
PGA, 0–4	3.0 (0.8)	–	676	2.9 (0.8)	–	257
Proportion of patients with PGA > 1	–	94.8	676	–	92.6	257
DLQI	11.5 (7.7)	–	672	11.7 (8.3)	–	256
Proportion of patients with DLQI > 10	–	50.6	672	–	52.4	256
Scalp-PGA	2.0 (1.4)	–	675	1.9 (1.3)	–	256
Proportion patients with scalp involvement[a]	–	78.1	675	–	80.5	256
Nail-PGA	0.6 (1.0)	–	676	0.7 (1.0)	–	257
Proportion patients with nail disease[a]	–	36.5	676	–	37.4	257
Palmoplantar-PGA	0.7 (1.2)	–	676	0.7 (1.2)	–	257
Proportion patients with palmoplantar psoriasis[a]	–	30.8	676	–	32.7	257
Itch NRS	5.0 (2.9)	–	660	4.7 (2.9)	–	253
Proportion patients with itch NRS ≥ 3	–	75.8	660	–	73.1	253

BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; NRS, numerical rating scale; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; SD, standard deviation

[a]Nail, palmoplantar, and scalp involvement was assumed if the respective PGA was mild, moderate, severe, or very severe at baseline

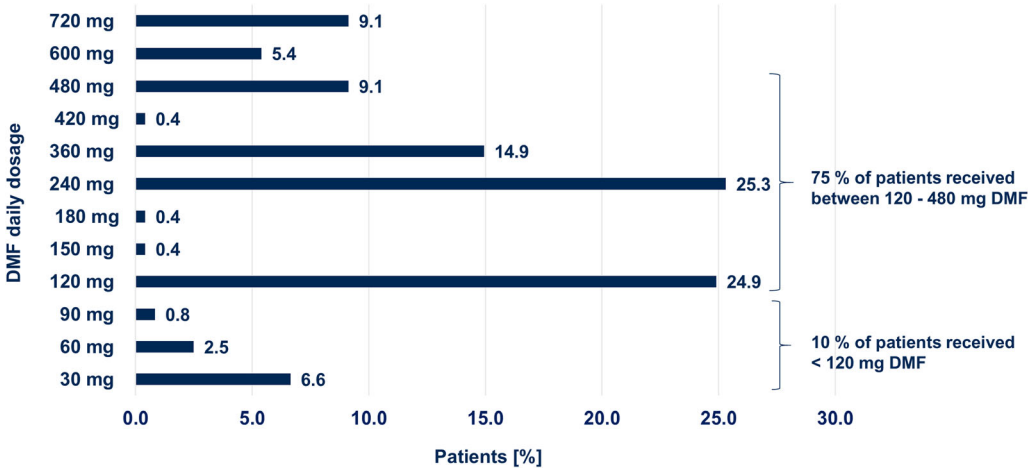

Fig. 1 Maintenance dose of DMF at week 52. Distribution of daily DMF dose at week 52 (observed cases, OC, $n = 241$); dose per tablet: 30 mg and 120 mg. Treatment with DMF is initiated at 30 mg once daily and escalated further up to a maximum dose of 720 mg per day, taking into account individual tolerability and treatment response

9.1–11.3, $p < 0.001$) for LOCF (see Fig. S1 in the electronic supplementary material).

The mean absolute PASI was 14.6 (95% CI 13.9–15.3) for OC at baseline, improving to 3.0 (95% CI 2.5–3.6, $p < 0.001$) after 52 weeks. For LOCF, it was 14.4 (95% CI 13.5–15.3) at baseline and 5.0 (95% CI 4.4–5.5, $p < 0.001$) after 52 weeks. This corresponds to a mean reduction of 79.5% (OC) and 65.7% (LOCF) (Fig. 2a). The proportion of patients achieving PASI < 3 and PASI < 5 increased accordingly ($p < 0.001$, Fig. 2b). These improvements are also reflected in the PASI 50 and PASI 75 response (data not shown). For OC, these were 80.0% (95% CI 74.4–84.8%) PASI 50 responder and 63.3% (95% CI 56.9–69.3%) PASI 75 responder at week 52. For LOCF, these were 69.0% (95% CI 64.6–73.2%) and 51.0% (95% CI 46.3%–55.6%), respectively.

Impactful Areas

The mean nail-PGA of patients with nail disease at baseline (nail-PGA > 0) improved from 1.8 (95% CI 1.7–1.9) at baseline to 0.6 (95% CI 0.4–0.8, $p < 0.001$) at week 52 for OC (Fig. 3a). After 52 weeks of DMF treatment, 56.8% (95% CI 43.0–58.1%) of the patients presenting with nail disease at baseline were clear with a nail-PGA of 0 (Fig. 3b). For LOCF, it improved from 1.8 (95% CI 1.6–1.9) at baseline to 0.8 (95% CI 0.7–1.0, $p < 0.001$) at week 52 (Fig. 3a). Of the patients presenting with nail involvement at baseline, 50.6% (95% CI 46.3–67.0%) were clear (nail-PGA of 0) at week 52 (Fig. 3b), and 70.2% of patients experienced an improvement of their nail involvement until week 52 (see Fig. S2a in the electronic supplementary material).

For patients with palmoplantar psoriasis at baseline (PP-PGA > 0), the mean PP-PGA improved from 2.3 (95% CI 2.1–2.4) at baseline to 0.8 (95% CI 0.5–1.0, $p < 0.001$) at week 52 for OC (Fig. 3c). At week 52, 57.3% (95% CI 44.3–61.3%) of the patients were clear with a PP-PGA of 0 (Fig. 3d). For LOCF, it improved from 2.2 (95% CI 2.1–2.4) to 0.9 (95% CI 0.7–1.1, $p < 0.001$) at week 52 (Fig. 3c), with 52.9% (95% CI 45.9–68.2%) of the patients being clear (PP-PGA of 0) at week 52. Improvements in palmoplantar disease were reported for 57.3% of the patients after 52 weeks of DMF treatment (see Fig. S2b in the electronic supplementary material).

Scalp involvement also improved up to week 52. The proportion of patients with scalp-PGA 0/1 (clear/almost clear) was 37.5% (95% CI 33.8–41.3%) at baseline, and 79.8% (95% CI 74.4–84.6%, $p < 0.001$) at week 52 for OC (Fig. 4). For LOCF, these were 36.6% (95% CI 32.3–41.1%) and 69.3% (95% CI 64.9–73.4%, $p < 0.001$), respectively, at week 52 (Fig. 4).

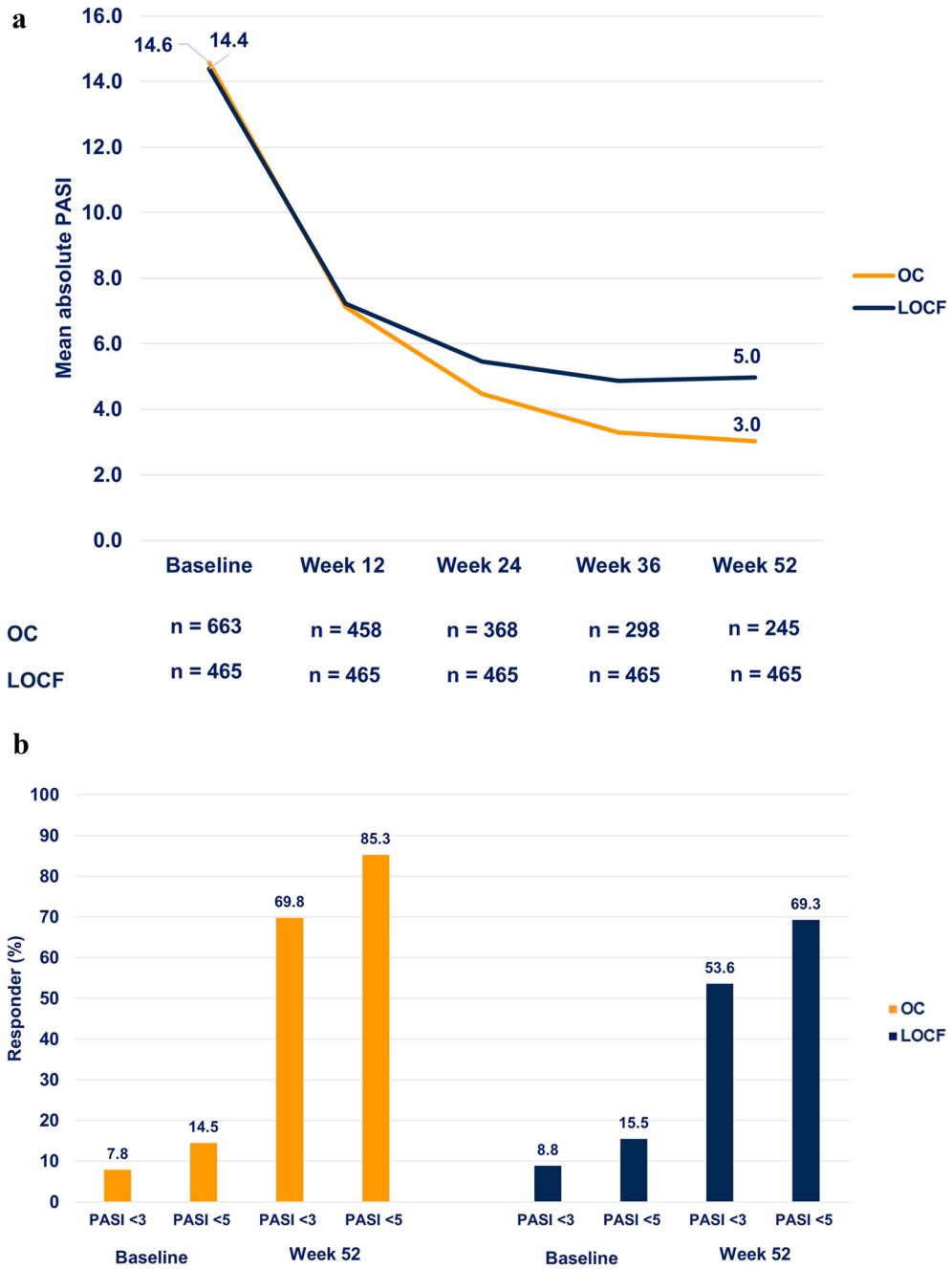

Fig. 2 **a** Absolute PASI from baseline to week 52. $p < 0.001$ versus baseline, using OC and LOCF, Wilcoxon signed-rank test. **b** Proportion of patients with PASI < 3 and PASI < 5. $n = 663$ (OC baseline), $n = 245$ (OC week 52), $n = 465$ (LOCF); $p < 0.001$ versus baseline for PASI < 3 and PASI < 5, using OC and LOCF, McNemar's test. LOCF, last observation carried forward; OC, observed cases; PASI, Psoriasis Area and Severity Index

Assessment of Pruritus

The proportion of patients with no or only mild pruritus/itch (itch NRS < 3) increased from baseline to week 52 from 24.2% (95% CI 21.0–27.1%) to 76.9% (95% CI 71.2–82.0%, $p < 0.001$). For LOCF, it increased from 23.9% (95% CI 20.1–28.0%) to 61.5% (95% CI 57.0–65.9%, $p < 0.001$) (see Fig. S3 in the electronic supplementary material).

Treatment Satisfaction

Patients' and physicians' ratings of treatment satisfaction was very good or good in 94.6% of the patients and 95.5% of the physicians for effectiveness, and 87.7% and 92.6%, respectively, for tolerability.

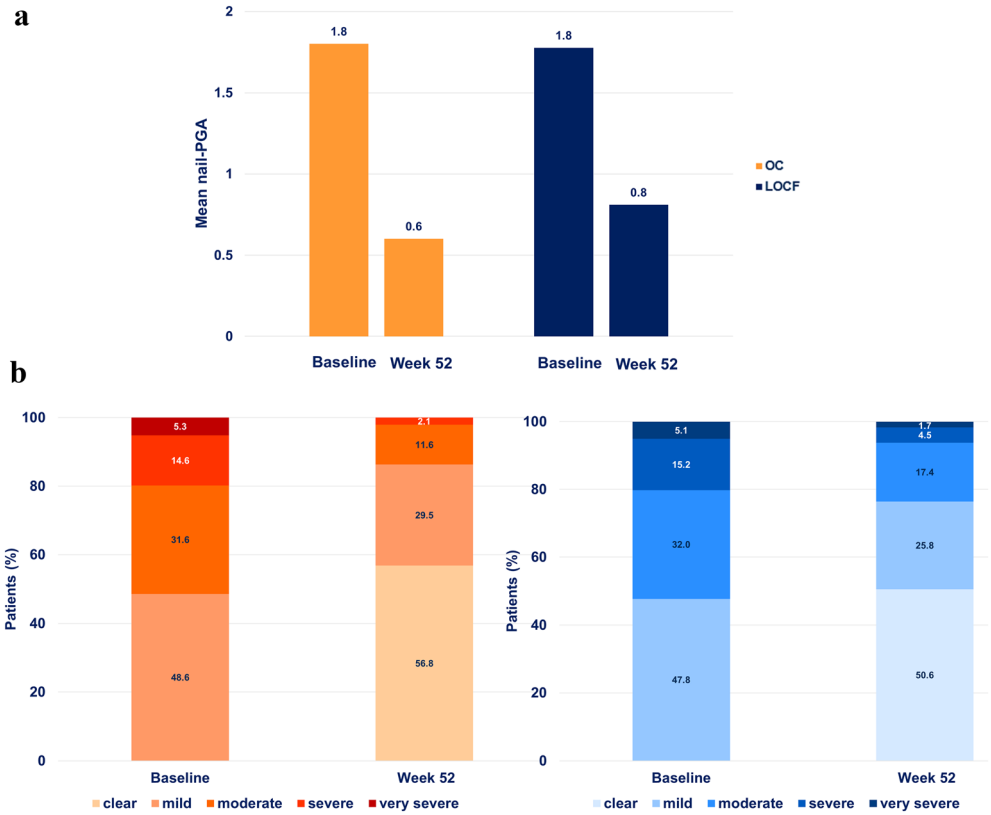

Fig. 3 **a** Physician's Global Assessment of nail psoriasis. Patients presenting with nail disease at baseline (nail PGA > 0 at visit 1) $n = 247$ (OC baseline), $n = 95$ (OC week 52), $n = 178$ (LOCF); $p < 0.001$ versus baseline, using OC and LOCF, McNemar's test. **b** Physician's Global Assessment of nail psoriasis—distribution of nail severity grades. Patients presenting with nail disease at baseline (nail PGA > 0 at visit 1), $n = 247$ (OC baseline), $n = 95$ (OC week 52) in red on the left, $n = 178$ (LOCF) in blue on the right, $p < 0.001$ for clear or mild nail disease versus baseline, McNemar's test. **c** Physician's Global Assessment of palmoplantar psoriasis. $n = 205$ (OC baseline), $n = 82$ (OC week 52), $n = 140$ (LOCF); $p < 0.001$ versus baseline, using OC and LOCF, McNemar's test. **d** Physician's Global Assessment of palmoplantar psoriasis—distribution of degrees of severity of palmoplantar psoriasis. Patients presenting with palmoplantar disease at baseline (PP-PGA > 0 at baseline), $n = 205$ (OC baseline), $n = 82$ (OC week 52) in red on the left, $n = 140$ (LOCF) in blue on the right, $p < 0.001$ for clear or almost clear versus baseline, McNemar's test. LOCF, last observation carried forward; PP-PGA, palmoplantar Physician Global Assessment

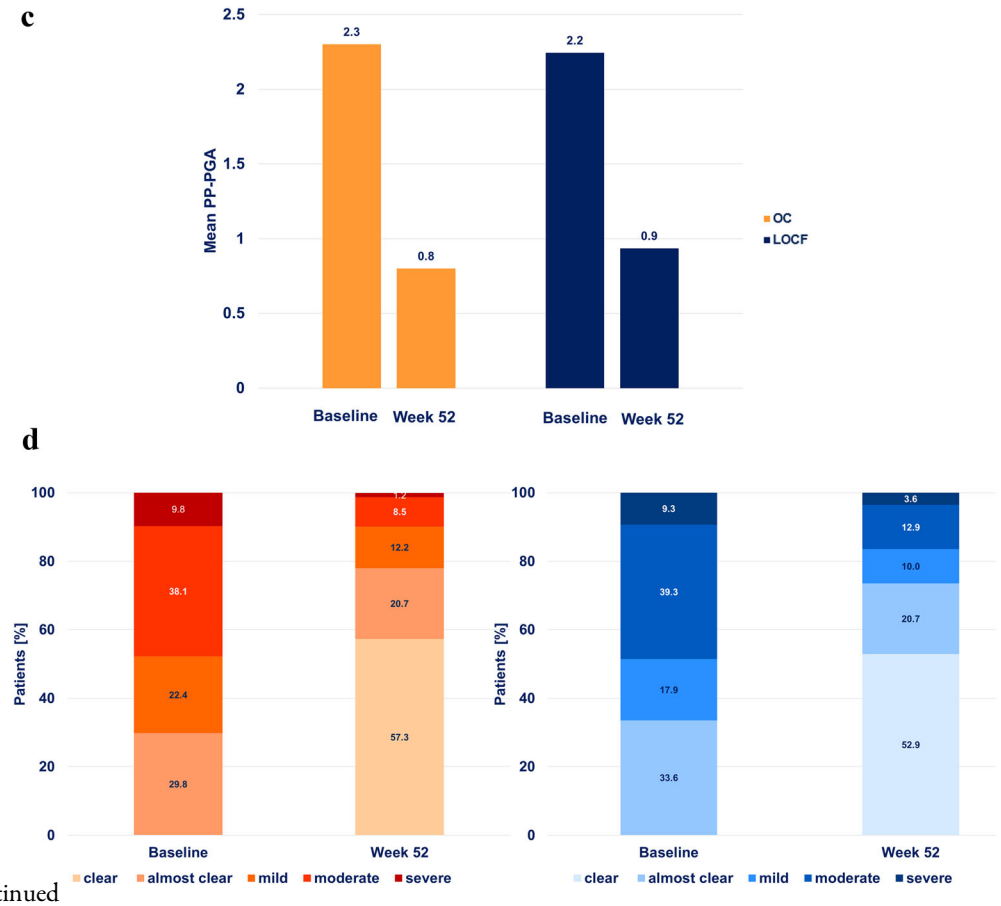

Fig. 3 continued

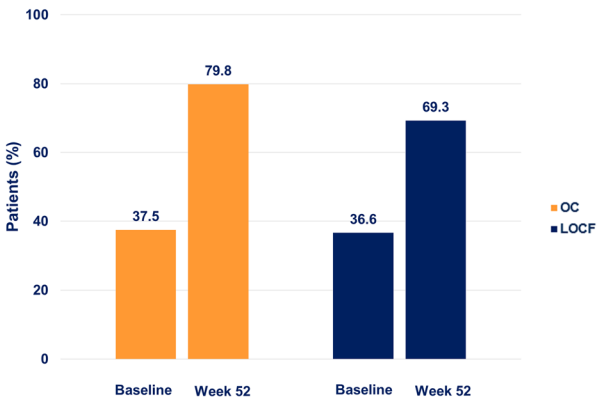

Fig. 4 Physician's Global Assessment of scalp psoriasis scalp-PGA 0/1 (clear or almost clear). $n = 675$ (OC baseline), $n = 253$ (OC week 52), $n = 452$ (LOCF); $p < 0.001$ versus baseline, using OC and LOCF, McNemar's test. LOCF, last observation carried forward; OC, observed cases; PGA, Physician Global Assessment

Safety

Top-ranking reasons provided for treatment discontinuation were intolerance (55.9%) and lack of efficacy (24.1%) (see Fig. S4 in the electronic supplementary material). However, in 5.0%, achievement of treatment goal was provided as a reason.

Overall, 479 ADRs and 21 SADRs occurred in 37.0% and 1.9% of the patients, respectively. Most frequently reported ADRs were diarrhea (11.8%), lymphopenia (10.5%), flush (8.0%), abdominal pain (7.5%), and pain in the upper stomach (6.2%). Most frequently reported SADRs were lymphopenia (0.7%), abdominal pain (0.3%), and diarrhea (0.3%).

DISCUSSION

Our current interim analysis of the SKILL NIS confirmed the high efficacy and good tolerability of DMF in patients suffering from moderate-to-severe chronic plaque psoriasis as observed in the phase III pivotal clinical trial and in the prior interim analysis at week 24 of the SKILL study [13, 14]. The good long-term efficacy and safety until 52 weeks of treatment was also seen in patients with psoriasis with involvement of the palmoplantar area, the scalp, and nails. About half of the patients with nail-PGA > 0 or PP-PGA > 0 at baseline were clear after 52 weeks of DMF treatment (50.6% and 52.9%, respectively). The proportion of patients with scalp-PGA 0/1 (clear/almost clear) significantly increased to 79.8% (OC) and 69.3% (LOCF, both $p < 0.001$). These results are promising and should be taken into account when choosing the treatment for patients suffering from involvement of impactful areas. Regarding nail involvement, indeed, these data corroborate findings from other studies, showing an improvement of Nail Psoriasis Severity Index in patients receiving FAE [15].

With regard to dose, it should be noted that 75% of the patients had a daily maintenance dose at week 52 between 120 and 480 mg, i.e., the majority of patients did not require the maximum daily dose of 720 mg (six tablets). Furthermore, 10% of the patients even used a very low maintenance dose (below a daily dose of 120 mg DMF). In comparison with the German PsoBest registry, where the mean maintenance dose of FAE was reported at 406.4 mg [16], the majority of patients thus needed a slightly lower DMF maintenance dose.

The interim data also showed significant improvements for pruritus/itch, with 76.9% (OC) and 61.5% (LOCF, both $p < 0.001$) of the patients showing no or only mild itch (NRS < 3) after 52 weeks of DMF treatment. Pruritus intensity in psoriatic patients has been linked to quality of life impairment, stigmatization, and depression [17].

A recent retrospective study including patients with moderate-to-severe psoriasis who had received DMF treatment during the coronavirus disease 2019 (COVID-19) pandemic has demonstrated that DMF is an effective treatment option also in patients who develop severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, with satisfying safety under routine care [18]. Furthermore, Esposito et al. [18] reported a clinically significant improvement in psoriatic lesions in impactful areas such as the scalp, genital, or face, which is in line with our data.

Overall, no unexpected findings were observed related to tolerability and safety, confirming the well-established profile of FAEs and, in particular, showing that DMF does not increase the risk of infections [5, 18–20].

Limitations of the study are its observational character and lack of a control group, as well that it was conducted exclusively in Germany. All reported outcomes were documented according to German routine dermatological practice, and data were not always available for all parameters. Measured variables may have been influenced by responder bias, i.e., patients experiencing a favorable treatment response may have been more likely to continue treatment, while those who were not experiencing a favorable treatment response may have tended to discontinue treatment. To address this shortcoming, in addition to OC, a more conservative imputation method has been used to carry forward less favorable results in patients with missing data/who terminated prematurely (LOCF). Treatment responder may have exhibited different disease characteristics than the total patient population. However, a comparison of baseline characteristics and disease severity did not reveal marked differences between patients with data at week 52 and the total population.

CONCLUSIONS

In conclusion, long-term DMF treatment (until 52 weeks) in the context of routine dermatological practice showed good overall effectiveness and tolerability as observed in clinical studies. Furthermore, a positive effect on plaque psoriasis-affected impactful areas such as nails, palmoplantar area and scalp, and reduction in psoriasis-related itch was shown.

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Compliance with Ethics Guidelines. The study received approval from Ethics Committee of the Hamburg Medical Association and was reported to the responsible federal authority, German National Association of Statutory Health Insurance Physicians, Central Federal Association of Health Insurance Funds and Association of Private Health Insurance e.V. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All subjects provided informed consent to participate in the study.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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