A multicentre open-label study of apremilast in palmoplantar pustulosis (APLANTUS)

D. Wilsmann-Theis,1,* C. Kromer,2 S. Gerdes,3 C. Linker,4 N. Magnolo,5 R. Sabat,6 K. Reich,7 R. Mössner2

1Department of Dermatology and Allergy, University of Bonn, Bonn, Germany
2Department of Dermatology, University Medical Center Göttingen, Göttingen, Germany
3Center for Inflammatory Skin Diseases, Department of Dermatology, University Medical Center Schleswig-Holstein Campus Kiel, Kiel, Germany
4TFS Clinic, TFS Trial Form Support GmbH, Hamburg, Germany
5Department of Dermatology, University Hospital Münster, Münster, Germany
6Psoriasis Research and Treatment Centre, Charité – Universitätsmedizin Berlin, Berlin, Germany
7Translational Research in Inflammatory Skin Diseases, Institute for Health Services Research in Dermatology and Nursing, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

*Correspondence: D. Wilsmann-Theis. E-mail: dagmar.wilsmann-theis@ukb.uni-bonn.de

Abstract

Background Palmoplantar pustulosis (PPP) is a chronic skin disease with painful erythematous scaly or crusty lesions and pustules on the palms and soles. Apremilast is a phosphodiesterase 4 inhibitor that has proven effective in the therapy of psoriasis, psoriatic arthritis and in oral ulcers associated with Behcet’s disease.

Objective To explore the efficacy of apremilast in PPP.

Methods APLANTUS was a phase 2 single-arm multicentre study of apremilast in 21 subjects with moderate-to-severe PPP. Primary endpoint was the per cent change of the Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI) at week 20 compared to baseline.

Results 20 weeks of oral treatment with apremilast in patients with moderate-to-severe PPP resulted in a significant decrease of the PPPASI with a median reduction of 57.1% (p < 0.001), and 61.9% of patients achieved at least a 50% improvement of the PPPASI relative to baseline. The total number of pustules per patient decreased significantly relative to baseline with 76.2% of patients achieving at least a 50% reduction in total pustules count at week 20. Improvement of PPP was also apparent in a significant decrease of the dermatologic life quality index (DLQI). The median DLQI score dropped from 8.5 at baseline to 2.0 at week 20 (p = 0.030). Apremilast was generally well tolerated, and no serious adverse events occurred.

Conclusions Patients with PPP treated with apremilast showed benefit both in objective and subjective disease parameters. Apremilast should be investigated further in this difficult-to-treat skin condition.

EudraCT number: 2016-005122-11.

Received: 1 February 2021; Accepted: 21 April 2021

Conflicts of interest

D. Wilsmann-Theis has been an advisor, speaker or investigator for Abbvie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, Leo Pharma, Eli Lilly, Medac, Merck Sharp & Dohme Corp., Novartis, Pfizer, UCB Pharma and VBL. C. Kromer has been an advisor, speaker or investigator for Janssen-Cilag and Novartis Pharma. S. Gerdes has been an advisor and/or received speakers’ honoraria and/or received grants and/or participated in clinical trials of the following companies: AbbVie, Affibody AB, Akari Therapeutics Plc, Almirall-Hermal, Amgen, Anaptys Bio, AstraZeneca AB, Baxalta, Bayer Health Care, Biogen Idec, Bioskin, Boehringer-Ingelheim, Celgene, Centocor, Dermira, Eli Lilly, Foamix, Forward Pharma, Galderma, Hexal AG, Incyte Inc., Isotechnika, Janssen-Cilag, Johnson & Johnson, Kymab, Leo Pharma, Medac, Merck Serono, Mitsubishi Tanabe, Mölnlycke Health Care, MSD, Neubourg Skin Care GmbH, Novartis, Pfizer, Polichem SA, Principia Biopharma, Regeneron Pharmaceutical, Sandoz Biopharmaceuticals, Sanofi-Aventis, Schering-Plough, Sienna Biopharmaceuticals, Takeda, Teva, Trevi Therapeutics, UCB Pharma and Vascular Biogenics. N. Magnolo has served as advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Almirall, Asana, Biogen, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Dermira, Dr. Reddy’s Laboratories, Eli Lilly, Galapagos, Galderma, Genentech, Incyte, Janssen, Kyowa Kirin, etc.
LEO Pharma, Novartis, MSD, Pfizer, Regeneron, Sun Pharma and UCB. R. Mössner has been an advisor and/or received speakers’ honoraria and/or received grants and/or participated in clinical trials of the following companies: Abbvie, Almirall, Amgen, Biogen IDEC GmbH, Boehringer-Ingelheim, Celgene, Essex Pharma GmbH, Janssen-Cilag GmbH, Leo Pharma GmbH, Lilly, Merck Serono GmbH, MSD SHARP & DOHME GmbH, Novartis Pharma GmbH, Pfizer GmbH and UCB. C Linker participated in clinical trials sponsored by Abbvie, Affibody, Almirall, Amgen, Avillion, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Centocor, Covagen, Derma, Forward Pharma, Galapagos, GlaxoSmithKline, Janssen-Cilag, Kyowa Kirin, Leo, Lilly, Medac, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharma and UCB. K. Reich has served as advisor and/or paid speaker for and/or participated in clinical trials sponsored by Abbvie, Affibody, Almirall, Amgen, Avillion, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Centocor, Covagen, Derma, Forward Pharma, Fresenius Medical Care, Galapagos, GlaxoSmithKline, Janssen-Cilag, Kyowa Kirin, Leo, Lilly, Medac, Merck Sharp & Dohme, Novartis, Mlltenyi Biotec, Ocean Pharma, Pfizer, Regeneron, Samsung Bioepis, Sanofi, Sun Pharma, Takeda, UCB, Valeant and Xenoprot.

Funding sources
This work was supported by a research grant from Celgene. The funding source had no role in the design of this study, its execution, analysis or interpretation of data or decision to submit results.

Introduction
Palmoplantar pustulosis (PPP) is a chronic-inflammatory disease with erythematous scaly and crusty lesions on the palms and/or soles, typically associated with pustules in different stages of evolution. The phenotype can occur in conjunction with plaque-type psoriasis, but also as the only disease manifestation. The concept that PPP represents a disease entity with a pathophysiology different from classical psoriasis is supported by its different genetic background and relative resistance to targeted therapies that show high response rates in plaque-type disease (reviewed in1). PPP is painful, associated with functional impairment and a negative impact on the quality of life.2 Acitretin with or without psoralen plus UVA (PUVA), cyclosporine, methotrexate and biologics are all used with varying degrees of success, and there remains a significant unmet therapeutic need.

Apremilast is a small-molecule oral inhibitor of the phosphodiesterase 4 (PDE4) leading to an intracellular accumulation of cyclic adenosine monophosphate (cAMP) with a subsequent shift towards an anti-inflammatory cytokine profile.3 Apremilast is approved in the European Union for the treatment of adult patients with plaque-type psoriasis and psoriatic arthritis (PsA). It has recently been approved for the treatment of oral ulcers in Behçet’s disease. Case reports have shown promising outcomes of apremilast therapy for PPP.4–7 Here, we report the clinical findings of a single-arm open-label investigator-initiated trial of apremilast for the treatment of PPP over 20 weeks.

Methods

Trial design
The primary aim of this phase II study was to explore the clinical response of PPP patients to apremilast. Secondary aims included its effect on Dermatology Life Quality Index (DLQI) and the evaluation of safety.

Eligible patients were 18 years or older, had a diagnosis of PPP for at least 6 months, with moderate-to-severe disease as defined by a Palmoplantar Pustulosis Area and Severity Index (PPASI) ≥ 12, who were eligible for systemic therapy, with or without concomitant plaque psoriasis. Patients were excluded if they had been treated with an anti-psoriatic biologic in the past 2 years or had received apremilast previously. Other antipsoriatic systemic therapies and PUVA phototherapy had to be discontinued at least 28 days before baseline visit; topical antipsoriatic therapy and UVB phototherapy had to be discontinued 14 days before baseline visit.

The primary endpoint was the per cent change of PPPASI at week 20 compared to baseline. Secondary endpoints included absolute and per cent change of PPPASI and of the DLQI over time. Exploratory endpoints included the number of patients with an at least 50% and 75% reduction in the number of pustules compared to baseline, respectively, and the change of pain and itch as determined by Visual Analogue Scale (VAS) over the past week relative to baseline. The methodology of severity scoring for PPPASI and pustules counts are shown in the Supplementary data (Tables S1 and S2).4 Safety assessments included blood pressure and pulse rate assessments at each visit and a complete physical examination performed at baseline and week 20.

As data on the natural course of PPP patients were very limited, the number of patients in this very rare disease was oriented on other pilot trials in rare diseases. In case the primary endpoint was reached, data from this trial were intended to serve as basis for the design of controlled trials with apremilast in PPP in the future.8
All patients gave informed consent for participation in the study. The study (EudraCT 2016-005122-11) was approved by local ethical review boards and was conducted according to the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki.

Interventions
Patients were treated with apremilast for 20 weeks in the dosing schedule approved for plaque-type psoriasis. Accordingly, the dose of apremilast was gradually increased from 10 mg/day by 10 mg/day, until, from day 6 onwards, the final dose of 30 mg twice daily was reached.

**Table 1** Baseline characteristics of the PPP Intention-to-Treat Population

| Characteristic                  | No. (total:21) |
|--------------------------------|----------------|
| Age, mean (SD), years          | 59.8 (9.3)     |
| Female                         | 16 (76.2%)     |
| Body mass Index, mean (SD)     | 27.2 (4.2)     |
| Bodyweight, mean (SD), kg      | 78.1 (15.6)    |
| Northern European              | 20 (95.2%)     |
| Age at onset of disease, mean (SD), years | 52.1 (13.6)   |
| Psoriasis vulgaris             | 6 (28.6%)      |
| Psoriatic arthritis            | 3 (14.3%)      |
| Smoking status                 |                |
| Current smoker                 | 15 (71.4%)     |
| Ex-Smoker                      | 4 (19.0%)      |
| Never-Smoker                   | 2 (9.5%)       |
| PPPASI, mean (SD)              | 17.7 (5.3)     |
| Pustules count, mean (SD)      | 41.3 (50.8)    |
| VAS pain, mean (SD)            | 40.0 (32.8)    |
| VAS itch, mean (SD)            | 36.3 (27.4)    |
| DLQI mean (SD)†                | 9.8 (6.2)      |

**Previous therapies:**

| Patients with prior phototherapy | 11 (52.4%) |
| UVB-therapy                      | 3 (14.3%)  |
| PUVA-therapy (psoralen applied topically) | 8 (38.1%) |
| Patients with prior systemic therapy‡ | 14 (66.7%) |
| Methotrexate                     | 7 (33.3%)  |
| Systemic retinoid                | 7 (33.3%)  |
| Cyclosporin                      | 3 (14.3%)  |
| Fumaric acid esters              | 1 (4.8%)   |
| Mycophenolate mofetil            | 1 (4.8%)   |
| Prednisolone per os              | 1 (4.8%)   |
| Biologic                         | 0          |

DLQI, Dermatology Life Quality Index; PPPASI, Palmoplantar Pustulosis Area and Severity Index; SD, Standard deviation; VAS, Visual Analogue Scale.

†One baseline value missing.
‡10 patients had one, and 2 patients 2 and another 2 patients 3 different prior systemic therapies, respectively.

**Figure 1**
(a) Box plot of Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI) values of patients (intention-to-treat analysis, last observation carried forward) over the study period. The line in the middle of the box represents the median, the lower and upper margins of the box represent the 25th and 75th percentiles, and the ends of the whiskers represent the upper and lower adjacent values (which are the most extreme values within Q3+1.5*(Q3-Q1) and Q1-1.5*(Q3-Q1), respectively). + denotes the mean, and asterisks denote a significant difference (p < 0.001) of PPPASI percent change relative to baseline. (b) Proportion and absolute number of patients (intention-to-treat analysis, last observation carried forward) who achieved at least a 50% and 75% improvement of the PPPASI, respectively. Intention-to-treat analysis with non-responder imputation led to the same results. (c) Proportion and absolute number of patients (intention-to-treat analysis, last observation carried forward) who achieved at least a 50% and 75% reduction in the palmoplantar pustules count, respectively. Intention-to-treat analysis with non-responder imputation led to the same results. (d) Change in PPPASI at 20 weeks apremilast therapy versus disease duration. The amount of PPPASI reduction inversely correlates with the disease duration, rs= 0.619; p = 0.003.

**Statistical analysis**
Analyses of primary, secondary and exploratory clinical endpoints were based on the intention-to-treat population with
missing values imputed using the Last Observation Carried Forward (LOCF) method. Statistical analyses and creation of figures were performed using the Stata v15.0 version. Statistical comparison between treatment and baseline values was done based on the Wilcoxon signed-rank test with two-sided \( p \)-values <0.05 indicating significance. There was no correction for multiple testing. Analysis of correlations was based on Spearman’s rank-order correlations. Correlation of disease duration with per cent change in PPPASI was performed as post hoc analysis.

**Results**

**Patients**

A total of 21 patients were enrolled and received treatment in five German dermatological centres starting November 2018, of whom 20 patients completed the full course of interventions by August 2019 (Figure S1). One patient terminated the study early due to diarrhoea and nausea, a treatment-related adverse event (TEAE). Baseline demographics and clinical characteristics are
summarized in Table 1. 6 out of 21 patients had concomitant plaque-type psoriasis, and 3 had a diagnosis of PsA. The mean (SD) baseline PPPASI was 17.7 (5.3), and the mean (SD) DLQI was 9.8 (6.2). In 9/21 patients, according to DLQI, there was a very large or extremely large effect on patient’s life. The majority of patients (14/21) had received at least one systemic therapy previously.

Clinical outcomes
The primary endpoint of the study was met with a significant reduction of the PPPASI at week 20 compared to baseline with a median improvement (Q1, Q3) of 57.1% (41.3%, 69.8%; p < 0.001). Absolute PPPASI values are depicted in Fig. 1a. The proportion of patients achieving a PPPASI50 and PPPASI75 response at week 20 were 13/21 (61.9%) and 3/21 (14.3%), respectively (Fig. 1b). Analysis of exploratory endpoints showed a significant reduction of the total pustules count from baseline at all time points. The median reduction (Q1, Q3) at week 20 was 76.3% (53.4%, 100%; p < 0.001). A strong effect was already apparent at week 4, with 61.9% of patients achieving an at least 50% reduction in total pustules count at this time point; this percentage increased to 76.2% at week 20 (Fig. 1c). The PPPASI reduction at week 20 relative to baseline inversely correlated with disease duration, (rS=0.619; p = 0.003) (Fig. 1d). Representative examples of the clinical response of PPP to apremilast are shown in Fig. 2.

Parallel to the clinical improvement, the median DLQI (Q1, Q3) declined from 8.5 (5.0, 15.3) at baseline to 3.0 (1.0, 12.0) at week 12 (p = 0.005) and 2.0 (1.0, 13.0) at week 20 (p = 0.030) (Fig. 3a). We also observed a rapid onset of pain reduction; the median VAS (Q1, Q3) dropped from 31 (11, 67) at baseline to 4 (0, 19) at week 4, and to 2 (0, 27) at week 12 (Fig. 3b). The median itch VAS (Q1, Q3) decreased from 31 (13, 55) at baseline to 12 (6, 49) at week 20 (p = 0.092) (Fig. 3c).

Safety
A total of 58 TEAE occurred in 19 patients, which were mostly of mild intensity. 14 patients presented with TEAEs considered by the investigator to be related to apremilast treatment. The majority of drug-related TEAEs were gastrointestinal disorders. The highest TEAE rate was observed for nausea in 6 out of 21 patients, followed by diarrhoea, nasopharyngitis and headache in 5 patients each. The only two severe TEAEs that occurred, both considered related to treatment, were diarrhoea and nausea in one patient each, the latter leading to the only early treatment discontinuation observed in this study.

Discussion
PPP is a rare and painful chronic skin disease, which is often recalcitrant to therapy. Only acitretin has a label for this condition in Europe. Recently, guselkumab has shown efficacy in prospective clinical trials in PPP, with PPPASI50 responses of up to 60% at week 16.11,12, which, however, is small compared to its efficacy in plaque psoriasis. In the present exploratory study apremilast met the primary endpoint and showed a significant reduction of the PPPASI at week 20 compared to baseline. Furthermore, PPPASI reductions were also significant at all other time points during the study. PPPASI50 and PPPASI75 responses were achieved at week 20 by 61.9% and 14.3% of the patients, respectively. Interestingly, apremilast was more effective in patients with short disease duration.

Probably, the effect of apremilast in PPP is mediated by the inhibition of the infiltration of neutrophils into skin, in fact, the number of pustules on palms and soles dropped rapidly in this study. Such an effect may also contribute to the effect of apremilast on oral ulcers in Behcet’s disease which is also considered a neutrophilic dermatosis.
In our study, apremilast was generally well tolerated and no new safety events were observed. Gastrointestinal disorders, mostly nausea and diarrhoea, were the most frequently observed TEAEs, in line with the known safety profile of apremilast. Limitations of this study include its small sample size and the non-randomized, open-label design. PPP is a disease with an often undulating disease severity, and a considerable clinical improvement in the placebo arm has been observed in previous PPP trials. Thus, it is possible that some of the clinical improvement of PPP under apremilast therapy in this study is attributable to spontaneous improvement of disease severity.

In conclusion, in this open-label trial apremilast showed a rapid and significant clinical improvement of PPP that requires replication and validation in larger controlled studies. It will be interesting to further dissect the mechanisms involved in the possible effect of apremilast in neutrophilic dermatoses.

Acknowledgement

The patients in this manuscript have given written informed consent to publication of their case details.

Author contributions

KR was sponsor of the study. DWT, KR, RS and RM designed the study. DWT, CK, SG, CL, NM, KR and RM cared for the patients, and all authors analysed and interpreted the data, DWT, CK, KR and RM wrote the first draft of the manuscript and all authors gave their approval for the final manuscript.

References

1. Misiak-Galazka M, Zozula J, Rudnicka I. Palmoplantar pustulosis: recent advances in etiopathogenesis and emerging treatments. Am J Clin Dermatol 2020; 21: 355–370.
2. Wilsmann-Theis D, Jacobi A, Frambach Y et al. Palmoplantar pustulosis – a cross-sectional analysis in Germany. Dermatol Online J 2017; 23.
3. Schafer PH, Parton A, Capone L et al. Apremilast is a selective PDE4 inhibitor with regulatory effects on innate immunity. Cell Signal 2014; 26: 2016–2029.
4. Carrascosa de Lome R, Conde Montero E, La Cueva Dobao P de. Refractory palmoplantar pustulosis successfully treated with apremilast. Dermatol Ther 2020; 33: e13230.
5. Eto A, Nakao M, Furue M. Three cases of palmoplantar pustulosis successfully treated with apremilast. J Dermatol 2019; 46: e29–e30.
6. Haebich G, Kalavala M. Successful treatment of refractory palmoplantar pustulosis with apremilast. Clin Exp Dermatol 2017; 42: 471–473.
7. Kromer C, Wilsmann-Theis D, Gerdes S et al. Drug survival and reasons for drug discontinuation in palmoplantar pustulosis: a retrospective multicenter study. J Dtsch Dermatol Ges 2019; 17: 503–516.
8. Bhushan M, Burden AD, McBhime K et al. Oral liarozole in the treatment of palmoplantar pustular psoriasis: a randomized, double-blind, placebo-controlled study. Br J Dermatol 2001; 145: 546–553.
9. Haynes D, Strunk Jl, Topham CA et al. Evaluation of ixekizumab treatment for patients with pityriasis rubra pilaris. JAMA Dermatol 2020; 156: 668.
10. Hongbo Y, Thomas CL, Harrison MA et al. Translating the science of quality of life into practice: what do dermatology life quality index scores mean? J Invest Dermatol 2005; 125: 659–664.
11. Terui T, Kobayashi S, Okubo Y et al. Efficacy and safety of guselkumab, an anti-interleukin 23 monoclonal antibody, for palmoplantar pustulosis: a randomized clinical trial. JAMA Dermatol 2018; 154: 309–316.
12. Terui T, Kobayashi S, Okubo Y et al. Efficacy and safety of guselkumab in Japanese patients with palmoplantar pustulosis: a phase 3 randomized clinical trial. JAMA Dermatol 2019; 155: 1133.
13. Puig L. Guselkumab for the treatment of adults with moderate to severe plaque psoriasis. Expert Rev Clin Immunol 2019; 15: 589–597.
14. Hatemi G, Mahr A, Ishigatsubo Y et al. Trial of apremilast for oral ulcers in Behçet’s syndrome. N Engl J Med 2019; 381: 1918–1928.
15. Irla N, Navarini AA, Yawalkar N. Allitrretinoin abrogates innate inflammation in palmoplantar pustular psoriasis. Br J Dermatol 2012; 167: 1170–1174.
16. Mrowietz U, Bachelez H, Burden AD et al. Secukinumab for moderate-to-severe palmoplantar pustular psoriasis: results of the 2PRECISE study. J Am Acad Dermatol 2019; 80: 1344–1352.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Patient disposition flow chart.

Tables S1–S2 Efficacy Assessments: methodology of severity scoring for Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPASI) (Table S1) and Pustules count (Table S2).