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Research Article

Impact of a Dispenser in Acne Therapy - "PUMP It" Study with 1,388 Patients

Uwe Gieler[1*], Eva Milena Peters[2], Volker Streit[3], Inés Rojo Pulido[4], Doris Porombka[4], Andreas Jäckel[4]

[1]Clinic for Dermatology, Venereology and Allergology, University of Giessen, Gießen, Germany

[2]Department of Psychosomatic Medicine, Psychoneuroimmunology Laboratory, University of Giessen, Gießen, Germany

[3]Dermatologist in Private Practice, Buchholz in der Nordheide, Germany

[4]Galderma Laboratorium GmbH, Düsseldorf, Germany

[*]**Corresponding author:** Uwe Gieler, Universitätsklinikum Gießen und Marburg GmbH, Klinik für Dermatologie, Venerologie and Allergologie, Gaffkystr. 14, 35392 Gießen, Germany. Tel: +4964198543200; Email: uwe.gieler@psycho.med.uni-giessen.de

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Abstract

Because daily dosage is difficult to achieve in topical acne therapy, a dispenser was developed to ensure the delivery of a pre-measured amount (0.5 mL) of adapalene 0.1% / benzoyl peroxide 2.5% (adapalene-BPO). This non-interventional study assessed application and convenience of a pump dispenser, treatment adherence, efficacy and safety under daily practice conditions. The included patients (≥ 9 years) with moderate to severe acne received adapalene-BPO in the pump. Assessments were carried out at baseline and after 3 to 12 weeks of treatment. Overall, 1,388 patients were enrolled, and facial acne severity improved in 96.9% of patients. Application was described as easy and time-saving and89.6% of patients used the acne gel regularly. Dysmorphic concerns were reported in 5.6% of acne patients. Adapalene-BPO dispensed from the pump is easy to apply, simplifies acne treatment and leads to good treatment adherence in patients with moderate to severe inflammatory acne.

Introduction

Acne is one of the most frequent skin diseases in dermatological practice and the primary reason for consulting a dermatologist [1]. The onset occurs mainly during puberty but also during adolescence, thus affecting approximately 85% of the 11- to 30-year olds [2]. Acne is a chronic inflammatory skin disease, predominantly affecting the face where it is difficult to hide. With less frequent incidence the back (60%) and the chest (15%) may also be involved [3]. The negative influence of acne symptoms with regard to self-esteem is often neglected in the management of acne [4], although body dysmorphic concerns due to disfigurement by acne have been observed [5].

Due to the multifactorial etiology of acne which includes follicular hyper keratinization, increased sebum production, bacterial proliferation and inflammation [6-9], treatment with a combination therapy of agents with complementary mechanisms has become the standard first-line therapeutic approach [3]. Adapalene 0.1% / benzoyl peroxide 2.5% (adapalene-BPO) is the first antibiotic-free fixed-dose combination gel approved for the once-daily topical treatment of acne [10,11]. The fixed combination adapalene/BPO attacks three out of the four major pathogenic factors of acne: abnormal desquamation, *Propionibacterium acnes* (*P. acnes*) hyperproliferation and inflammation [10]. BPO is the most potent bactericidal agent, being more effective than topical antibiotics against *P. acnes* and thus indirectly anti-inflammatory in addition to keratolytic properties [12]. Safety and efficacy of adapalene-BPO in the short- and long-term management of moderate to severe acne have been confirmed in several clinical and observational studies [13-20]. The rapid onset of action and a particularly favourable tolerability profile compared with other retinoids are attributes that can potentially promote patient adherence, an important factor in treatment success [21,22]. In addition to convincing efficacy and good tolerability, adherence to a medication is supported by easiness of application [12]. Therefore, a dispenser with a standardized dosage was developed and tested in this study. The pump system delivers a pre-measured amount

of 0.5 mL gel with each actuation, allowing a more consistent dosage compared to a tube. Furthermore, application of consistent doses from a dispenser allows physicians to calculate the therapy duration with the prescribed compound and to monitor if the patient has followed the agreed therapy regimen [23]. A recent open label study revealed a high degree of patient satisfaction with the pump compared to the tube [24]. The present non-interventional study "PUMP it" was conducted in order to evaluate if the favorable assessment of the pump also applies under real-life conditions.

Methods

Study Design and Setting

In this multicenter, open-label, prospective non-interventional observational study application and convenience of adapalene-BPO dispensed from the pump were evaluated as well as treatment adherence, efficacy, safety and body dysmorphic concerns. This study was conducted at 170 centers in Germany between January and September 2015. Depending on the individual patient visits observation time per patient was 3 to 12 weeks.

Data were recorded at baseline and at the follow-up visit. Patients were free to withdraw from the study at any time and for any reason.

This non-interventional observational study (according to §4 (23) AMG [Medicinal Products Act]) was conducted in accordance with the joint recommendations for the planning, conducting and analyzing of observational studies compiled by the Federal Institute for Drugs and Medical Devices (BfArM) and the Paul Ehrlich Institute (PEI) (edition of July 7, 2010). It was reviewed and approved by federal state law established Ethics Committees Counseling of the Faculty of the Medicine University of Giessen (No: 221/14) and has therefore been performed in accordance with the ethical standards laid down in the Declaration of Helsinki passed in 1964 and its later amendments. No diagnostic or therapeutic measures, exceeding the already necessary scope were required and treatment routine was not altered by this non-interventional, observational study. All patients (respectively their legal guardians) provided their written informed consent prior to entering the study.

Participants

Patients aged ≥9 years with moderate to severe inflammatory facial acne, corresponding to grade 4 to 12 according to the Leeds Revised Acne Grading System defined for the face (grade 0 to 3: mild, grade 4 to 7: moderate, grade 8 to 10: moderately severe, grade 11 to 12: very severe) [25] were selected from dermatology practices. Criteria for study participation were that topical therapy of acne with adapalene-BPO was indicated and that the decision about treating the patient with adapalene-BPO dispensed from the pump device was made independently from this study. Concomitant use of moisturizing skin care products was allowed. Pregnancy or breastfeeding, prevalence of acne inversa, preferential manifestation of microcysts, macrocysts or macro comedones and hypersensitivity to the medication or any of the ingredients were criteria for non-selection. Selection of patients was subject of the investigator's discretion. The physicians were obliged to include and to document consecutively the first appropriate patients fitting the selection criteria defined in the study protocol, in order to reduce the risk of bias. Solely the participating investigators determined regimen, dose and duration of adapalene-BPO treatment. In line with the common clinical acne treatment practice, the follow-up visit was scheduled between 3 and 12 weeks after starting initial treatment up to the individual decision of the dermatologist regarding daily practice. Since adapalene-BPO is an approved medicinal product, patients obtained advice on dosing and application from the package leaflet, in addition to verbal advice provided by the physician during the routine consultation.

Assessments

The primary efficacy variable was facial acne severity according to the revised Leeds grading system at follow-up. The primary endpoint was change in acne severity from baseline to follow-up. In order to ensure a standardized assessment, all investigators were provided with an illustration of the Leeds scale with the study protocol to evaluate acne severity grade. Secondary variables were changes in acne severity on chest and back and patient-reported assessment of application and convenience of adapalene-BPO dispensed from the pump device, including rating of handling, hygiene, issues and satisfaction on a 5-point Likert scale (strongly agree, agree, neither agree nor disagree, disagree, strongly disagree) and overall assessment on a 6-point scale (very good, good, satisfactory, sufficient, poor, insufficient) at follow-up. Physicians rated the handling of the pump on a 5-point Likert scale (strongly agree, agree, neither agree nor disagree, disagree, strongly disagree) and general assessment on a 6-point scale (very good, good, satisfactory, sufficient, poor, insufficient) at follow-up. Adherence was assessed at follow-up by patient-reported frequency of the application. Safety and tolerability were assessed through evaluation of Adverse Drug Reactions (ADR) documented at the follow-up visit.

Statistical Analyses

All data analyses were carried out according to a pre-established analysis plan. The collected data were analyzed descriptively with epidemiological methods, using the SPSS (IBM Deutschland GmbH, Ehningen, Germany) for Windows program package (Version 22.0). For continuous variables, statistical parameters including arithmetic mean, standard deviation and range were calculated. Frequency distributions for discrete variables were provided as percentage in relation to the total sample. Free text answers were transferred post-hoc into adequate

coding schemes and analyzed as frequency distribution. Evaluation of parameters measuring the clinical course were performed by intra individual difference analysis (first vs. last examination) using the Wilcoxon signed-rank test. Difference was calculated per patient and subsequently averaged. Patients with missing data for one or both variables were not imputed. For post-hoc analyses of variables affecting efficacy, subgroups were compared using Mann-Whitney-U-Test. Predictors were analyzed using linear regression. Correlations were calculated using Pearson correlation. Odds ratios were estimated using Mantel Haenszel statistics. All tests were two-sided and significance was declared at the 0.05 level. Clinical improvement was defined as decrease of ≥1 degree on the revised Leeds scale.

Results

Patient Disposition and Baseline Characteristics

In total, 1,388 patients from 170 centers were enrolled and all were included in the analysis. Mean (±SD) follow-up time was 49.5 ± 24.6 days. Baseline characteristics are summarized in Table 1. Slightly more female patients (58.6%) participated in the "PUMP it" study. Median age of patients was 19.0 years (range 9-61) and median age at onset of acne was 14.0 years (Range: 1-60). Marginally more than half of the patients (53.5%) had a positive family history of acne. The majority of patients (77.9%) suffered from facial acne grade 4 to 6 at baseline. In 44.2% of patients, acne was limited to the face. Both, chest and back were additionally affected in 29.5% of patients, while 6.0% and 12.7% had either chest or back involvement, respectively. In total, 11.6% of patients had concomitant diseases. Most frequent were diseases of skin and subcutaneous tissue (5.2%), followed by diseases of the respiratory system (2.1%). About half of the population (51.7%) received acne treatment within the last three months before study start. 11.7% had been treated previously with adapalene-BPO dispensed from the tube, while 41.6% received another regimen. The previous treatments most frequently administered were topical (15.2%) and oral (11.2%) antibiotics, followed by BPO (9.5%) and azelaic acid (8.6%). The reason for treating 155 patients with oral antibiotics was severity of facial acne (74.2%) and involvement of chest or back (39.4%).

Variable	n (%)
Gender	
Male	570 (41.1%)
Female	814 (58.6%)
Not documented	4 (0.3%)
Age (years)	
Mean (±SD)	21.0 ± 7.8
Median (Range)	19.0 (9-61)
Age at onset of acne (years)	
Median (Range)	14.0 (1-60)
Known family history of acne	743 (53.5%)
Severity of facial acne according to the Leeds revised acne grading system	
4	441 (31.8%)
5	366 (26.4%)
6	267 (19.2%)
7	151 (10.9%)
8	93 (6.7%)
9	27 (1.9%)
10	28 (2.0%)
11	3 (0.2%)
12	2 (0.1%)
Not documented	10 (0.7%)
Facial scars (multiple answers)	
None	749 (54.0%)
Patients with ≥1 kind of scars	585 (42.1%)
Atrophic	341 (24.6%)
Ice pick scars	168 (12.1%)
Hypertrophic	117 (8.4%)
Keloids	36 (2.6%)
Not documented	54 (3.9%)

Table 1: Baseline demographics (n=1,388).

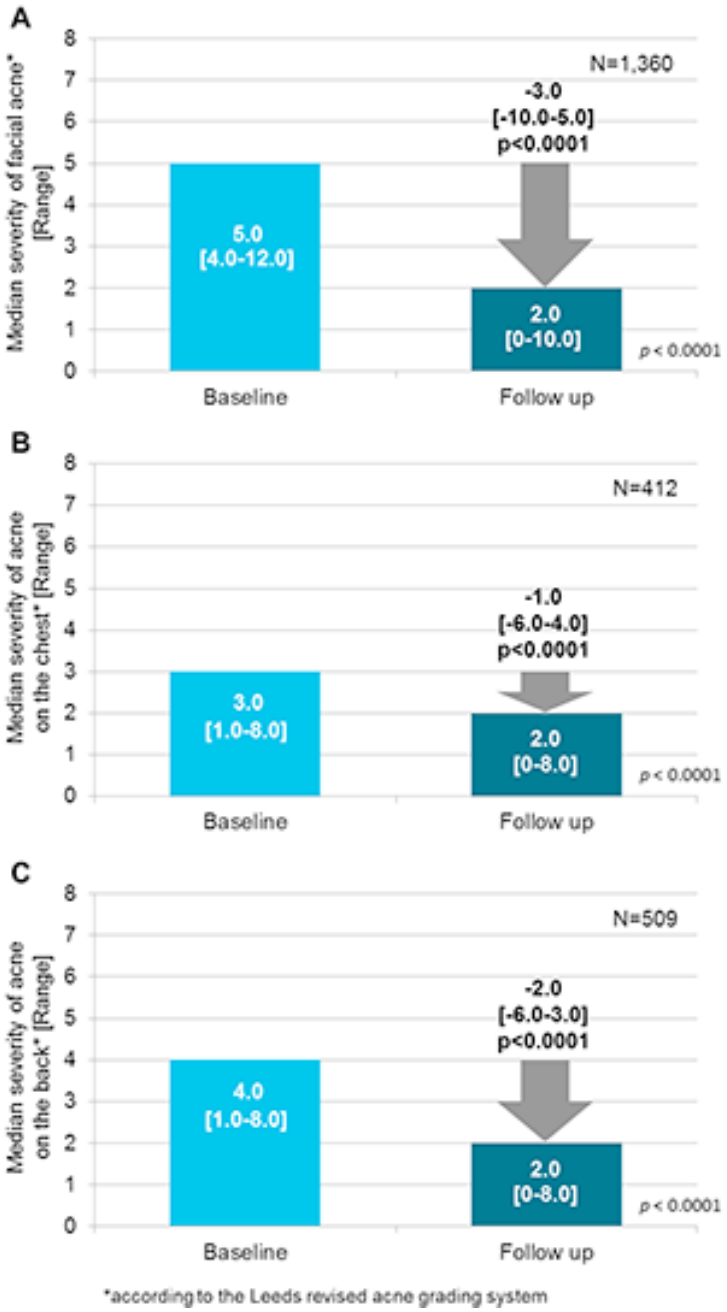
Treatment with Adapalene-BPO

For most patients (68.9%) the prescribed adapalene-BPO dosage for facial acne was one actuation per application. Additional topical treatment of chest and/or back was intended in 38.2% of patients. According to patient reported data, application on the back consisted mostly of one (15.5%) or two (9.4%) actuations, while 11.7%, 15.1%, and 4.7% of patients used one, two, or three actuations on the back, respectively. About two thirds of patients (67.7%) administered adapalene-BPO alone, while 26.3% received a combination treatment, consisting predominantly of oral (11.2%) and topical (7.0%) antibiotics. Additionally, moisturizing skin care or skin cleanser products were used in 64.7% and 75.8% of cases, respectively. The most commonly reported reason (31.1%) for switching to adapalene-BPO was insufficient efficacy of the previous regimen.

Efficacy

Over the study period, the majority of patients (94.9%) showed improvement in facial acne of at least one grade on the revised Leeds scale. During adapalene-BPO application, the median severity was reduced significantly from 5.0 to 2.0 ($p<0.0001$) on the revised Leeds scale (Figure 1A). At the follow-up visit, absence of any visible lesions was observed in 5.9% of patients. A subgroup analysis comparing the treatment success in patients receiving adapalene-BPO monotherapy versus combination treatment with oral antibiotics revealed that addition of oral antibiotics to the

treatment regimen did not cause an additional effect on the change in Leeds grade (p=0.228). Using linear regression, acne severity at baseline was identified as a significant predictor of treatment response (r=-0.479; p<0.001). Pretreatment had a strong tendency to predict treatment response, but did not reach statistical significance (r=0.044; p=0.051). Neither age nor gender had an impact on treatment response. Significant improvements were also observed after applying adapalene-BPO on chest (Figure 1B) and back (Figure 1C). Acne on the chest or back was completely resolved in 17.2% and 11.3% of patients at the follow-up visit, respectively. Physicians assessed the overall treatment with adapalene-BPO as good or very good in the majority of cases (95.4%).



Figures 1(A-C): Change in severity of facial acne **(A)** and truncal acne on chest **(B)** and back **(C)** according to the revised Leeds scale. Ranges (min/max) are given in brackets.

Treatment Adherence and Assessment of the Pump Dispenser

The majority of patients (89.6%) reported having used the gel regularly. Physicians and patients described the application of adapalene-BPO via the pump dispenser as easy and time-saving (Figure 2). Regarding the majority of patients, physicians agreed that the patient can easily understand how to use adapalene-BPO in the pump (97.3%) and that the consistent release of a defined amount of gel per actuation is a relevant advantage of the pump compared to the tube (96.8%). Accordingly, physicians stated that they tendto prescribe a pump device more frequently in the future (95.8%). More than 90% of patients preferred adapalene-BPO in the pump dispenser. Other attributes rated positive by the majority of patients included absence of dripping or leaking (96.0%) and design of the dispenser (74.6%). Overall, the majority of patients (93.1%) rated adapalene-BPO in the dispensing device as good or very good.

Safety

No serious adverse events were reported during the course of the study. In total, 20 ADRs (irritation, n=5; erythema, n=3; dryness, n=3; pruritus, n=2; swelling, n=2; rough skin, pain, burning, eczema) were documented in 10 patients. Adapalene-BPO was discontinued in 8 of these patients. ADRs resolved after adapalene-BPO was discontinued, suspended or reduced in dosage.

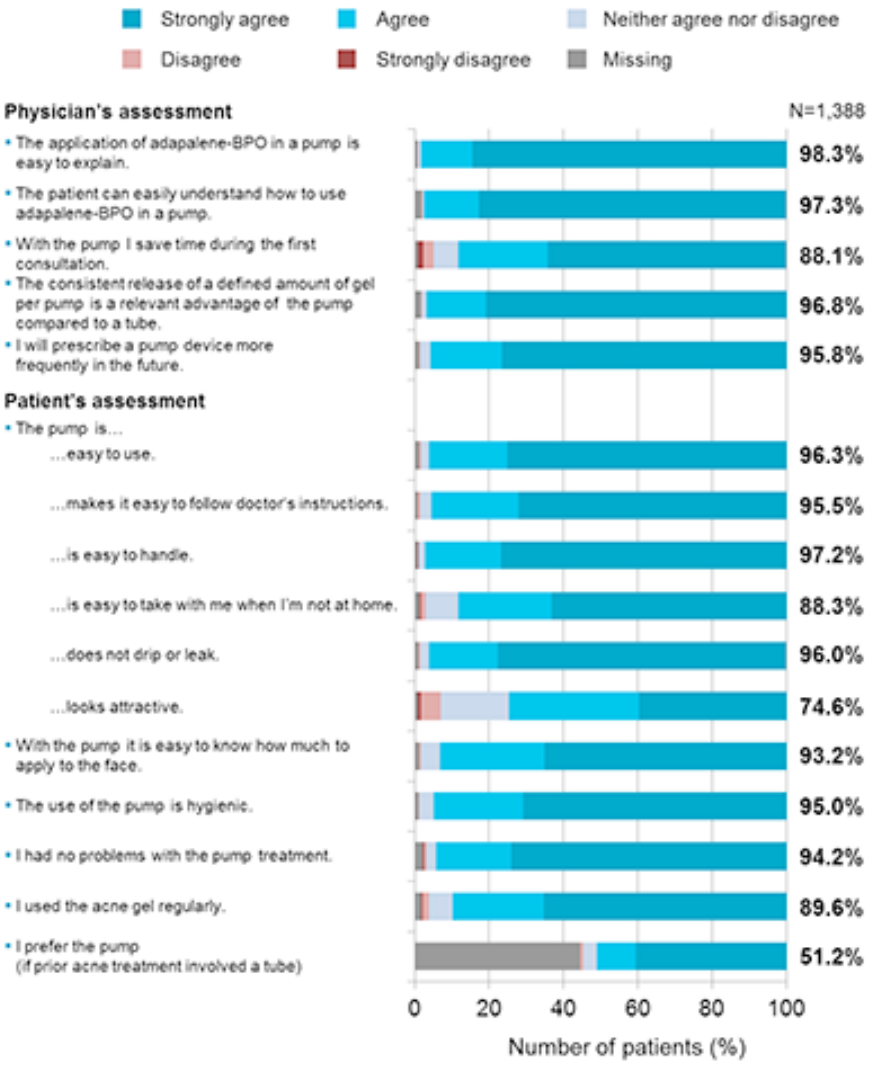


Figure 2: Physician's and patient's assessment of the adapalene-BPO pump dispenser. The values indicate the cumulated percentage for "agree" and "strongly agree".

Discussion

The present non-interventional study "PUMP it" was conducted to assess adapalene-BPO in a pump dispensing device with regard to application, convenience, treatment adherence, efficacy and safety in patients with moderate to severe inflammatory acne. The pump dispenser was developed in order to facilitate daily use and to ensure equal amounts of gel being applied in order to increase treatment adherence. According to the patients, benefits of the pump dispenser included effortless handling and application, cleanliness and easiness to follow the doctor's instructions. Consistently, physicians appreciated the time-saving effect during the consultation resulting from the easiness to explain the application. Furthermore, physicians regarded the consistent release of a defined amount of gel per pump as a relevant advantage of the pump dispenser compared to the tube. These results from a real-world setting confirm data obtained in a head-to-head comparison conducted under controlled conditions [24].

Adherence to acne regimen is a well-known issue, particularly in the population of adolescents and young adults [12,26]. Once-daily application and a fixed-dose gel formulation have already been established as key factors to enhance treatment adherence [12]. Consequently, good adherence was found in the majority of patients using adapalene-BPO from the tube under daily practice conditions [19,27]. An earlier phase IV study demonstrated that 95% of acne patients using a pump dispenser over a 3-months period took 75%-100% of their prescribed doses [30]. Therefore, a high degree of adherence was expected with the use of adapalene-BPO distributed from a dispensing device as well. Correspondingly, 89.6% of patients from our study confirmed using an adequate dose of adapalene-BPO on a regular basis.

Appropriate amounts of gel delivery compared to a possible over-application with a tube may not only enhance efficacy, but also reduce the occurrence of adverse events [23]. Here, the rate of reported ADRs was considerably low compared to previous studies conducted with the tube [19,20] which may be a consequence of consistent and adequate dosing with the pump dispenser. Nevertheless, due to the non-interventional character of this study reflecting real-life conditions, these findings need to be validated by controlled study data.

Overall, the treatment with adapalene-BPO led to significant improvement of facial acne in the majority of patients. At the follow-up visit acne severity had improved by at least one grade on the revised Leeds scale in 95% of patients, whereby 6% were entirely lesion-free. These results are consistent with data obtained from previous studies investigating adapalene-BPO dispensed from the conventional tube [13-20]. The heterogeneity of the treatment period ranging from 3 to 12 weeks with a medium duration of 6 weeks was a result of the non-interventional character of the study which was designed to reflect real-world data rather than enforcing a stringent follow-up period. However, subgroup analysis revealed that treatment response was independent of the length of observation period. This is in line with previous observations showing an onset of effect after 2 to 3 weeks [16,19,20]. Regardless of the early onset of treatment response, it is broadly accepted that due to the chronicity of acne, long-term treatment is required [12]. In this context, 9-month application of adapalene-BPO has been shown to further improve the facial clearance already achieved by short-term therapy by tripling the proportion of patients being free of visible lesions [20].

About one tenth of patients received oral antibiotics in addition to adapalene-BPO. While antibiotics have been a keystone in acne therapy for over 40 years, health authorities are urging all healthcare providers to limit antibiotic use in response to the development of widespread antibiotic resistance [29]. Yet, acne treatment with oral antibiotics is indicated in patients with severe acne or clinical manifestations on shoulders, chest or back [3]. Concurrently, most participating dermatologists prescribed concomitant antibiotics as consequence of acne severity or truncal acne presence. However, the addition of oral antibiotics to the treatment regimen did not have an effect on the outcome of facial acne in the present "PUMP it" study.

There is growing awareness that acne entails more than only cosmetic skin problems [4]. The impact on the patient's emotional well-being, social relationships and quality of life can be devastating, as manifested in reduced self-esteem, social embarrassment, social withdrawal and depression [30-38]. In this context, an evaluation of quality of life questionnaires showed that the impact of acne on quality of life did not correlate to the severity of the disease as assessed by the physician [30]. This discrepancy is captured by the Body Dysmorphic Disorder (BDD), an often under diagnosed comorbidity of acne [5].

The study is limited by its non-interventional design that allowed the use of concomitant acne medication as the physician deemed appropriate. Also, patient-reported outcomes were a potential limitation resulting in under- or overestimation and recall bias, particularly with regard to adherence and tolerability. However, the large number of patients ensures statistically conclusive data to provide a comprehensive profile of the clinical situation of acne patients in a real-world setting.

In conclusion, the results of this observational study "PUMP it" support the safe and effective use of ADA-BPO in the new pump dispenser in the management of patients with moderate to severe inflammatory acne. The severity grade of acne is significantly decreased within a short-term period. ADA-BPO in the new pump dispenser is easy to apply, simplifies acne treatment and leads to good treatment adherence.

Conflict of Interest

Prof Gieler has participated in acne-related clinical and experimental studies, symposia and advisory boards of Galderma Laboratorium GmbH, GSK-Stiefel GmbH, Almirall, Pierre Fabre and Bayer AG.

PD Dr. Eva Maria Peters declares no conflict of interest.

Dr. Volker Streit has participated in acne-relevant clinical studies and advisory boards of Galderma.

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