



Twice-weekly topical calcipotriene/ betamethasone dipropionate foam as proactive management of plaque psoriasis increases time in remission and is well tolerated over 52 weeks (PSO- LONG trial)

Mark Lebwohl, MD,^a Leon Kircik, MD,^a Jean-Philippe Lacour, MD, PhD,^b Monika Liljedahl, MD, PhD,^c Charles Lynde, MD, FRCPC,^{d,e} Marie Holst Mørch, MS,^c Kim A. Papp, MD, FRCPC, PhD,^f Jean-Luc Perrot, MD, PhD,^g Linda Stein Gold, MD,^h Amrit Takhar, MBChB, MRCP,ⁱ Diamant Thaçi, MD, PhD,^j Richard B. Warren, MBChB, FRCP, PhD,^k and Andreas Wollenberg, MD^l
New York, New York; Nice and St-Etienne, France; Ballerup, Denmark; Markham, Toronto, and Waterloo, Ontario, Canada; Detroit, Michigan; Wansford, Cambridgeshire and Manchester, United Kingdom; and Lübeck and Munich, Germany

Background: Topical psoriasis treatment relies on a reactive rather than a long-term proactive approach to disease relapse.

Objective: Assess long-term efficacy and safety of proactive psoriasis management with twice-weekly calcipotriene 0.005%/betamethasone dipropionate 0.064% (Cal/BD) foam.

Methods: Phase III trial (NCT02899962) included a 4-week open-label lead-in phase (Cal/BD foam once daily) and a 52-week, randomized, double-blind, maintenance phase. A total of 545 patients achieved treatment success (physician's global assessment "clear"/"almost clear," ≥ 2 -grade improvement from baseline) and were randomized to proactive management (Cal/BD foam; n = 272) or reactive management (vehicle foam; n = 273) twice-weekly, with rescue treatment of Cal/BD foam once daily for 4 weeks upon relapse. Primary endpoint was time to first relapse (physician's global assessment "mild" or higher).

From the Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York^a; the Department of Dermatology, University Hospital of Nice, Nice^b; LEO Pharma Ballerup^c; Lynde Dermatology, Probitry Medical Research, Markham^d; the Department of Medicine, University of Toronto^e; K. Papp Clinical Research, Waterloo^f; the Department of Dermatology, University Hospital of St-Etienne^g; the Department of Dermatology, Henry Ford Hospital, Detroit^h; Wansford and Kings Cliffe Practice, Wansfordⁱ; the Institute and Comprehensive Center for Inflammation Medicine, University of Lübeck^j; the Dermatology Centre, Salford Royal National Health Service Foundation Trust, Manchester National Institute for Health Research Biomedical Research Centre, University of Manchester^k; and the Department of Dermatology and Allergology, Ludwig Maximilian University Munich.^l

Funding sources: This trial was funded by LEO Pharma, Ballerup, Denmark. LEO Pharma supported the trial concept and design. Dr Warren is supported by the Manchester National Institute for Health Research Biomedical Research Centre.

Conflicts of interest: Dr Lebwohl is an employee of Mount Sinai and receives research funds from AbbVie Inc, Amgen, Arcutis Biotherapeutics, Boehringer Ingelheim, Dermavant Sciences Ltd, Eli Lilly and Company, Incyte, Janssen Research &

Development, LLC, LEO Pharma, Ortho Dermatologics, Pfizer, and UCB, Inc, and is a consultant for Aditum Bio, Allergan, Almirall, Arcutis Biotherapeutics, Avotres Therapeutics, Birch-BioMed Inc, BMD Skincare, Boehringer Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Castle Biosciences, Corrona, Dermavant Sciences, Evelo, Facilitate International Dermatologic Education, Foundation for Research and Education in Dermatology, Inozyme Pharma, Kyowa Kirin, LEO Pharma, Meiji Seika Pharma, Menlo, Mitsubishi, Neuroderm, Pfizer, Promius/Dr. Reddy's Laboratories, Serono, Theravance, and Verrica. Dr Kircik has served as an investigator, speaker, consultant, or an advisory board member for AbbVie Inc, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly and Company, LEO Pharma, Mayne Pharma, Novartis, Ortho Dermatologics Inc, Sun Pharmaceutical Industries Ltd, Arcutis Biotherapeutics, Dermavant Sciences Ltd, Pfizer, Dr Reddy's Laboratories, and UCB. Dr Lacour has received grants/research support as an investigator from AbbVie Inc, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Dermira, Galderma, Janssen Pharmaceuticals, Eli Lilly and Company, LEO Pharma, Merck, Novartis, Regeneron Pharmaceuticals, and Roche and has also received honoraria, advisory board, or consulting fees from AbbVie Inc, Bristol-Myers Squibb, Celgene, Galderma, Eli Lilly and Company,

Results: A total of 251 randomized patients (46.1%) completed the trial. Median time to first relapse was 56 days (proactive) and 30 days (reactive). Patients in the proactive group had an additional 41 days in remission compared with the reactive group over 1 year ($P < .001$). Number of relapses per year of exposure was 3.1 (proactive) and 4.8 (reactive). Cal/BD foam was well tolerated.

Limitations: Maintenance phase dropout rate (53.9%) was within the expected range but provides challenges in statistical analysis.

Conclusion: Long-term proactive management with Cal/BD foam demonstrated superior efficacy vs reactive management. (J Am Acad Dermatol 2021;84:1269-77.)

Key words: betamethasone dipropionate; calcipotriene; Enstilar; fixed-dose; foam; long-term; maintenance; proactive; psoriasis vulgaris; relapse; topical preparation.

Psoriasis vulgaris is a chronic, relapsing inflammatory disease¹ poorly categorized in time to relapse in relation to treatment.^{2,3} Treatment involves topical agents in mild to moderate disease and as adjuncts to phototherapy or systemic or biologic agents in moderate to severe disease.⁴ Long-term disease control is challenging, with many patients remaining untreated or undertreated.⁵

Currently, long-term management with topical treatment follows a reactive approach in response to disease relapses rather than a proactive approach to maintain remission.⁶ Proactive therapy with calcineurin inhibitors in atopic dermatitis has been an

CAPSULE SUMMARY

- Long-term disease control is challenging for patients with psoriasis. Current topical treatment follows a reactive approach to disease relapse.
- Long-term proactive management with calcipotriene/betamethasone dipropionate foam twice-weekly was more efficacious vs vehicle foam for prolonging time to first relapse, increasing time in remission, and reducing number of relapses.

emerging concept over the last decade⁷ that reduces, prevents, and delays disease exacerbations.⁸ Long-term trials bringing this concept to psoriasis are necessary to address the unmet need for effective and safe long-term management of psoriasis.

Fixed-dose combination calcipotriene 0.005%/betamethasone dipropionate 0.064% (Cal/BD) aerosol foam (Enstilar; LEO Pharma, Ballerup, Denmark) is approved in the United States (in adults and adoles-

cents) and in the European Union (in adults) for the treatment of psoriasis vulgaris for 4 weeks.^{9,10} In this trial, the efficacy and safety of long-term (52 weeks) twice-weekly proactive management with Cal/BD

LEO Pharma, Novartis, and Sanofi. Dr Liljedahl and author Mørch are employees at LEO Pharma. Dr Lynde has served as an investigator, speaker, consultant, or advisory board member for AbbVie Inc, Amgen, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Galderma, Janssen Pharmaceuticals, Eli Lilly and Company, LEO Pharma, Merck, Novartis, Regeneron Pharmaceuticals, Sanofi, Bausch Health, and Sun Pharmaceutical Industries Ltd. Dr Papp has received honoraria for advisory board, speaker, and consultant services from AbbVie Inc, Actelion, Allergan, Amgen, Anacor Pharmaceuticals Inc, Astellas Pharma, Avillion, Bausch Health, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermira, Eli Lilly and Company, EMD Serono, Galderma, Gilead, GlaxoSmithKline, Incyte Corporation, Janssen Pharmaceuticals, Kyowa Kirin, LEO Pharma, Meiji Seika, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Roche, Sanofi Genzyme, Sun Pharmaceutical Industries Ltd, Takeda Pharmaceutical Company, UCB Pharma, and Vertex Pharmaceuticals, and has received research grants for investigator services from AbbVie Inc, Actelion, Allergan, Amgen, Anacor Pharmaceuticals Inc, Astellas Pharma, Avillion, Bausch Health, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermira, Eli Lilly and Company, EMD Serono, Galderma, Gilead, GlaxoSmithKline, Incyte Corporation, Janssen Pharmaceuticals,

Kyowa Kirin, LEO Pharma, Meiji Seika, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Roche, Sanofi Genzyme, Sun Pharmaceutical Industries Ltd, Takeda Pharmaceutical Company, and UCB Pharma. Dr Perrot has been an advisor and/or received speakers honoraria and/or received grants and/or participated in clinical trials of the following companies: Abbott/AbbVie Inc, Amgen, Celgene, Eli Lilly and Company, Galderma, Incyte Corporation, Janssen-Cilag Ltd, Johnson & Johnson, LEO Pharma, Merck Serono, Merck Sharp & Dohme, Novartis, Pierre Fabre, Pfizer, Sanofi-Aventis, Schering-Plough, and UCB Pharma. Dr Stein Gold has been an investigator, speaker, consultant, or an advisory board member for AbbVie Inc, Amgen, Arcutis Biotherapeutics, Inc, Bristol-Myers Squibb, Celgene, Eli Lilly and Company, LEO Pharma, Mayne Pharma, Novartis, Ortho Dermatologics Inc, and Sun Pharmaceutical Industries Ltd. Author Takhar has received grants/research support and/or been a medical advisor for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cambridge and Peterborough Clinical Commissioning Group, Daiichi Sankyo, Dermal Laboratories, GlaxoSmithKline, LEO Pharma, Merck, Novartis, Pfizer, Roche, and Sanofi; Author Takhar has received grants/research support from National Institute of Health Research UK. Dr Traçi has been a consultant and advisor and/or received

Abbreviations used:

| | |
|---------|--|
| AEs: | adverse events |
| BSA: | body surface area |
| Cal/BD: | calcipotriene/betamethasone dipropionate |
| HPA: | hypothalamic pituitary adrenal |
| m-PASI: | modified Psoriasis Area and Severity Index |
| PGA: | Physician's Global Assessment |

foam was compared with vehicle foam in the prevention of disease relapse in adults with psoriasis.

METHODS

Trial design and interventions

This phase III, multicenter trial (NCT02899962) included a screening and washout phase of up to 4 weeks, a 4-week open-label lead-in phase, a 52-week randomized double-blind, vehicle-controlled maintenance phase, and an 8-week follow-up period (Supplementary Fig 1, available via Mendeley at <https://data.mendeley.com/datasets/27h89s5wpx/5>). The trial was conducted at 56 participating sites in the United States, Canada, United Kingdom, France, Poland, and Germany.

Eligible patients were ≥ 18 years, with truncal or limb psoriasis, or both, involving 2% to 30% of body surface area (BSA), physician's global assessment of disease severity (PGA) score of mild or higher (PGA ≥ 2) and modified psoriasis area and severity index (m-PASI) score ≥ 2 at baseline of the open-label lead-in phase (hereafter referred to as baseline). Patients were not eligible if they had received systemic treatment with biologic therapies with a possible effect on psoriasis within 4 to 16 weeks (depending on therapy) and systemic treatment with other

therapies with a possible effect on psoriasis within 4 weeks before baseline. A subgroup of these patients with 10% to 30% BSA and PGA moderate or higher (PGA ≥ 3) underwent hypothalamic pituitary adrenal (HPA)-axis testing at baseline, randomization, 28 weeks, and at the end of maintenance phase/early withdrawal.

Eligible patients who entered the open-label lead-in phase were instructed to apply Cal/BD foam once daily to psoriatic lesions on the trunk or limbs, or both, for 4 weeks. The purpose of this phase was to select responders to treatment. Treatment success was defined as a PGA score of clear/almost clear (PGA < 2) with ≥ 2 -grade improvement from baseline. Those who achieved treatment success entered the maintenance phase, and those who did not were discontinued at the end of the open-label lead-in phase. Patients were randomized 1:1 (stratified through an interactive web response system) to receive Cal/BD foam (proactive management group) or vehicle foam (reactive management group) twice-weekly (2 or 3 days apart on fixed days) for 52 weeks on psoriatic lesions that had cleared/almost cleared during the open-label lead-in phase or after treatment of a relapse (PGA score mild or higher).

During the maintenance phase, assessment for potential relapse occurred at clinic visits (every 4 weeks) and unscheduled visits as initiated by the patient. Upon relapse, patients from both treatment groups received rescue treatment with Cal/BD foam, applied to lesions once daily for 4 weeks. If a PGA score of clear/almost clear was regained after 4 weeks' rescue treatment, maintenance treatment was resumed; if not, patients were withdrawn from the trial.

Disease rebound was assessed during the 8-week follow-up period after the end of treatment/early

speaking fees and/or grants and/or served as an investigator in clinical trials for AbbVie Inc, Almirall, Amgen, Asana, Bioskin, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermira, DS Biopharma, Eli Lilly and Company, Galapagos NV, Galderma, Janssen-Cilag Ltd, Kymab, LEO Pharma, Merck MorphoSys AG, Novartis, Pfizer, Regeneron Pharmaceuticals, Roche, Sandoz, Sanofi, Samsung, Merck Sharp & Dohme Corp, and UCB. Dr Warren receives research grants from AbbVie Inc, Almirall, Amgen, Celgene, Janssen Pharmaceuticals, Eli Lilly and Company, LEO Pharma, Novartis, Pfizer, and UCB and is a consultant for AbbVie Inc, Almirall, Amgen, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Janssen Pharmaceuticals, LEO Pharma, Eli Lilly and Company, Novartis, Pfizer, Sanofi, and UCB. Dr Wollenberg has received grants, personal fees, or nonfinancial support from AbbVie Inc, Almirall, Beiersdorf, Bioderma, Chugai Pharmaceutical Co, Galapagos NV, Galderma, Hans Karrer, LEO Pharma, Eli Lilly and Company, L'Oréal,

Maruho Co, Ltd, MedImmune, Novartis, Pfizer, Pierre Fabre, Regeneron Pharmaceuticals, Sanofi-Aventis, and Santen.

IRB approval status: The protocol was approved by the Institutional Review Board or Independent Ethics Committee at each participating site. All patients provided written informed consent.

Accepted for publication September 8, 2020.

Correspondence and reprint requests to: Mark Lebwohl, MD, Department of Dermatology, 1 Gustave L. Levy Place, Box 1048, New York, NY 10029. E-mail: lebwohl@aol.com.

Published online September 18, 2020.

0190-9622

© 2020 by the American Academy of Dermatology, Inc. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jaad.2020.09.037>

withdrawal. Rebound was defined as an m-PASI ≥ 12 and an increase in m-PASI $\geq 125\%$ of the baseline value, or the development of new pustular, erythrodermic, more inflammatory psoriasis within 2 months of treatment discontinuation in the open-label lead-in phase, after discontinuation of once-daily rescue medication, or after the end of maintenance phase.

Further details on trial design, interventions, and changes to planned analyses are available in the Supplemental information.

Objectives

The primary objective was to compare the efficacy of Cal/BD foam as a twice-weekly proactive management treatment regimen with vehicle foam (reactive management), with Cal/BD foam as rescue treatment in the prevention of relapse. Secondary objectives were to evaluate other efficacy variables and the safety of long-term proactive management.

Endpoints

Primary endpoint was time to first relapse (PGA score mild or higher). Secondary endpoints were proportion of days in remission (PGA score “clear”/“almost clear”) and number of relapses. Exploratory endpoints were the number of active treatment days.

Additional safety assessments included adverse events (AEs), treatment-related AEs, incidence of disease rebound, local safety and tolerability (perilesional assessment at each visit for erythema, erosions, dryness and edema), and effect on calcium and corticosteroid metabolism.

Statistical methods

The dropout rate in a long-term trial with Cal/BD ointment was approximately 30% over 52 weeks.¹¹ We assumed that this would be the case in this trial and that between 4 and 8 relapses would occur per year in the vehicle group. A 30% reduction in hazard (ie, a hazard ratio of 0.7) for the proactive group relative to reactive group was considered of clinical interest. Based on a 2-sample survival test, 380 patients were planned to be randomized to obtain a power of 90% for a 5% significance level. According to the trial protocol and to comply with International Council for Harmonisation’s E1 regarding long-term safety, more patients were recruited and randomized to compensate for the dropout rate.¹¹

Time to first relapse was compared between treatment groups using a Cox proportional hazards model with treatment group, pooled sites, and disease severity at maintenance baseline as factors. The proportion of days in remission was analyzed by an analysis of variance model with treatment group,

pooled sites, and disease severity at maintenance baseline as factors, and multiple imputation was used for handling missing data for withdrawn participants. The predicted number of relapses was analyzed in a Poisson regression model with treatment group, pooled sites, disease severity at maintenance baseline as factors, participant as a random effect, and time at risk as an offset. For the primary and secondary endpoints, type 1 error was controlled by a hierarchical testing procedure. For the secondary endpoints, adjustment for multiplicity was done using the Holm-Bonferroni method.

Approval of the clinical trial protocol was obtained from the relevant Institutional Review Boards or Independent Ethics Committees and Regulatory Authorities, for each participating site, before patient enrollment. All patients provided written informed consent. The trial was conducted in accordance with Good Clinical Practice and Ethical Principles for Medical Research Involving Human Subjects.

RESULTS

Patients

Of 650 patients who entered the open-label lead-in phase, 521 (80.2%) achieved treatment success at week 4 and were randomized in the maintenance phase (full analysis set: proactive, $n = 256$; reactive, $n = 265$). A total of 24 patients (16 proactive, 8 reactive) who did not achieve treatment success at week 4 were randomized in error, thus 545 patients were included in the safety analysis set (proactive, $n = 272$; reactive, $n = 273$; Fig 1). There were 251 randomized patients (46.1%) who completed the 52-week maintenance period (Fig 1).

Baseline demographic and disease characteristics were similar between the groups (Table 1). Of those patients randomized, most had a PGA score of moderate at baseline (Table 1). Mean m-PASI at baseline was 7.9 (SD, 4.0) and 7.6 (SD, 3.7) for the proactive and reactive group, respectively, and mean BSA was 8.4% (SD, 6.4%) and 8.1% (SD, 6.3%), respectively (Table 1).

Efficacy

The PGA score at randomization to the maintenance phase was “clear” (proactive, $n = 54$ [21.1%]; reactive, $n = 56$ [21.1%]) or “almost clear” (proactive, $n = 202$ [78.9%]; reactive, $n = 209$ [78.9%]). Mean change from baseline to randomization in m-PASI and BSA in patients achieving treatment success during the open-label lead-in phase and included in the safety analysis set was -81.1% (SD, 17.9%) and -55.7% (SD, 38.2%), respectively.

During the maintenance phase, the estimated median time to first relapse from randomization

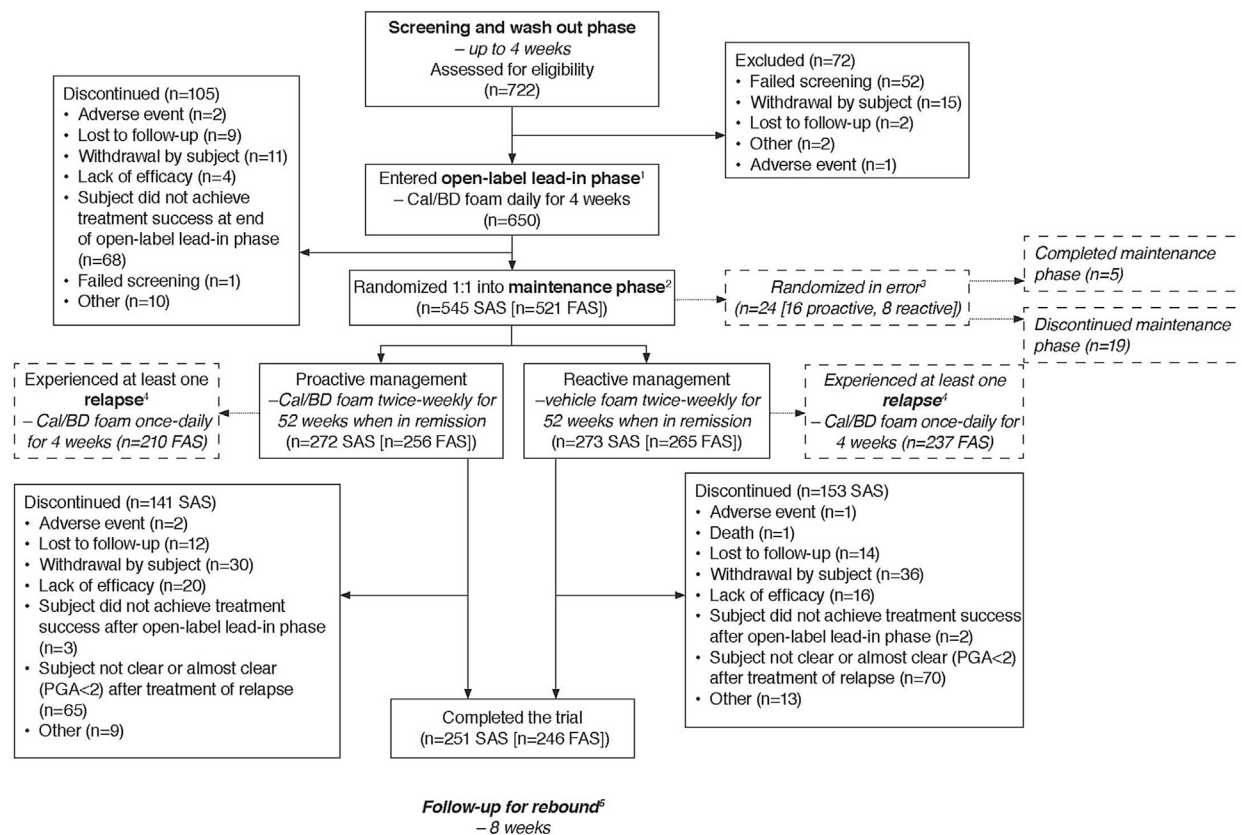


Fig 1. Consolidated Standards of Reporting Trials diagram of trial design and patient disposition. ¹All patients received topical calcipotriene/betamethasone dipropionate (Cal/BD) foam once daily for 4 weeks during the open-label lead-in phase. ²Treatment success was defined as a physician’s global assessment of disease severity (PGA) score “clear”/“almost clear” with ≥ 2 -grade improvement from baseline. ³Excluded from full analysis set (FAS). ⁴If a relapse (PGA at least “mild” [PGA ≥ 2]) occurred during the maintenance phase, rescue treatment (as separate rescue cans to apply to active lesions) was Cal/BD foam once daily for 4 weeks for both the proactive and reactive management groups. After 4 weeks of once-daily rescue treatment, patients who regained PGA <2 (“clear”/“almost clear”) restarted the twice-weekly maintenance treatment according to the original randomization scheme. Patients who did not regain a PGA score <2 (“clear”/“almost clear”) after 4 weeks of once-daily rescue medication were withdrawn from the trial. ⁵Rebound was defined as a modified psoriasis severity index score (m-PASI) ≥ 12 and an increase in m-PASI $\geq 125\%$ of the baseline value of the open-label phase, or the development of new pustular, erythrodermic, more inflammatory psoriasis within 2 months of entering the maintenance phase, within 2 months after a previous relapse, or within 2 months after the end of the maintenance phase. SAS, Safety analysis set.

was prolonged by 26 days for patients in the proactive group compared with the reactive group (56 days vs 30 days, respectively; Fig 2). The risk of experiencing the first relapse was reduced by 43% in the proactive vs the reactive management group (hazard ratio, 0.57; 95% confidence interval, 0.47-0.69; $P < .001$). Of those who completed the maintenance phase, 30 patients in the proactive group and 6 patients in the reactive group did not experience relapse. The proportion of days in remission was significantly higher for patients in

the proactive vs reactive group. The estimated treatment difference was 11% (95% confidence interval, 8%-14%; $P < .001$), corresponding to 41 extra days in remission over 1 year (Fig 3). The rate of relapse was 46% lower (95% confidence interval, 37%-54%; $P < .001$) in the proactive group vs the reactive group. The predicted number of relapses per year of exposure was 3.1 (proactive) vs 4.8 (reactive).

Both groups responded to rescue treatment with Cal/BD foam, with most of the patients achieving

Table I. Baseline characteristics

| Demographics and disease characteristics at baseline* | Patients assigned to treatment in open-label lead-in phase | Patients randomized in the maintenance phase | |
|---|--|--|--------------------------|
| | All patients (N = 650) | Proactive (n = 272) | Reactive (n = 273) |
| Sex | | | |
| Female | 226 (34.8) | 86 (31.6) | 87 (31.9) |
| Male | 424 (65.2) | 186 (68.4) | 186 (68.1) |
| Age, y | | | |
| Mean (SD) | 51.8 (14.2) | 52.5 (14.9) | 52.0 (13.7) |
| Minimum; maximum | 19.0; 84.0 | 19.0; 84.0 | 19.0; 84.0 |
| Body mass index, kg/m ² | | | |
| Mean (SD) | 29.5 (6.6) | 29.1 (6.0) | 29.5 (6.8) |
| Minimum; maximum | 16.1; 64.8 | 17.1; 50.5 | 16.1; 64.8 |
| Race [†] | | | |
| White | 584 (92.0) | 238 (89.8) | 249 (92.9) |
| Asian | 37 (5.8) | 22 (8.3) | 13 (4.9) |
| Black or African American | 9 (1.4) | 3 (1.1) | 4 (1.5) |
| Other | 5 (0.8) | 2 (0.8) | 2 (0.7) |
| Duration of psoriasis | | | |
| Mean (SD), years | 18.4 (13.7) | 18.8 (13.3) | 18.1 (13.9) [‡] |
| Minimum; maximum | 1.0; 74.0 | 1.0; 62.0 | 1.0; 74.0 |
| Physicians global assessment | | | |
| Mild | 83 (12.8) | 25 (9.2) | 33 (12.1) |
| Moderate | 509 (78.3) | 223 (82.0) | 224 (82.1) |
| Severe | 58 (8.9) | 24 (8.8) | 16 (5.9) |
| m-PASI | | | |
| Mean (SD) | 7.7 (3.9) | 7.9 (4.0) | 7.6 (3.7) |
| Minimum; maximum | 2.0; 32.4 | 2.0; 28.0 | 2.0; 19.2 |
| Body surface area, % | | | |
| Mean (SD) | 8.2 (6.4) | 8.4 (6.4) | 8.1 (6.3) |
| Minimum; maximum | 1.0; 38.0 | 1.0; 36.0 | 2.0; 38.0 |

m-PASI, Modified psoriasis severity index score.

*Data are presented as number (%) or as indicated otherwise. All baseline characteristics for all analysis groups were collected at baseline of the open-label lead-in phase, before treatment with fixed-dose combination calcipotriene 0.005%/betamethasone dipropionate 0.064% (Cal/BD) foam.

[†]Patients, N = 635; Ca/BD, n = 265; vehicle, n = 268.

[‡]Patients, n = 272.

PGA “clear”/“almost clear”, with an overall response of 75.9% and 81.0% in the proactive and reactive groups, respectively. Patients who did not achieve treatment success after rescue treatment were withdrawn from the study (n = 65 in the proactive group; n = 70 in the reactive group; [Fig 1](#)).

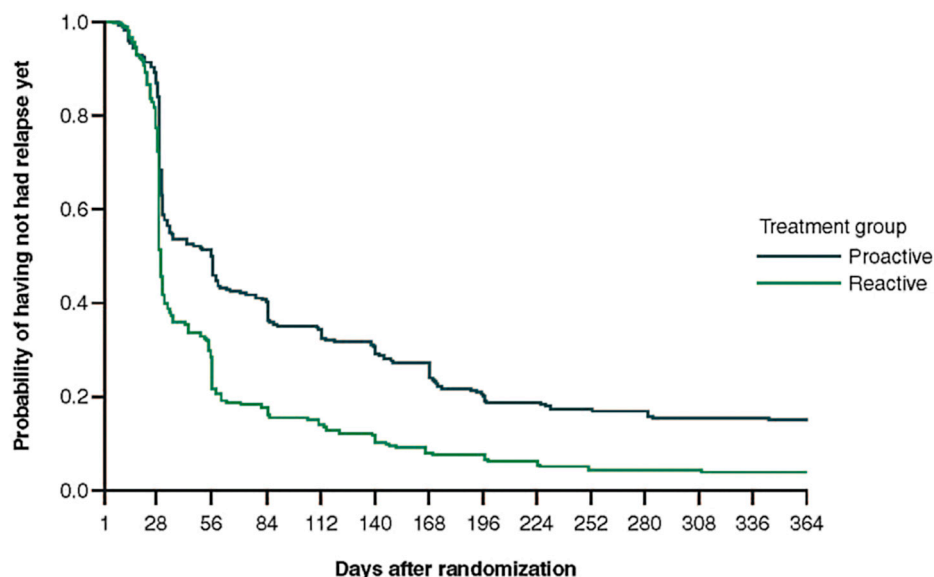
Safety

During the maintenance phase, the incidence of AEs was similar between treatment groups ([Table II](#)). The rate of AEs per 100 patient-years was 168.6 in the proactive group and 158.4 in the reactive group. The rate of serious AEs per 100 patient-years was low and similar (8.3, proactive; 7.9 reactive), as was the rate of treatment-related AEs (2.8, proactive; 4.5, reactive). The rate of severe AEs per 100 patient-years was 4.5 in the proactive group and 8.5 in the reactive group. AEs reported in >5% of patients were nasopharyngitis (8.1% proactive vs 7.0% reactive) and upper

respiratory tract infection (5.9% vs 5.5%), all of which were considered not related to the trial product by the investigator. Three patients (2 proactive [0.7%]; 1 reactive [0.4%]) experienced AEs leading to withdrawal. No AEs of skin atrophy were reported, and only 1 patient in the reactive management group had an AE of pruritus. Three patients (2 proactive and 1 reactive) had nonserious AEs that were adjudicated as related to long-term corticosteroid use (see the Supplemental information for further details).

The number of rebounds within 2 months of entering the maintenance phase was 6 in the proactive group and 7 in the reactive group. After a relapse, the number of rebounds was 4 in the proactive group and 17 in the reactive group. One patient in the reactive group experienced a rebound during the follow-up phase.

Most patients were within the normal ranges for serum and urinary calcium. No consistent



| | Number of patients at risk of relapse | | | | | | | | | | | | | |
|-----------|---------------------------------------|-----|-----|-----|----|----|----|----|----|----|----|----|----|-----|
| Proactive | 256 | 219 | 128 | 100 | 83 | 75 | 65 | 47 | 41 | 36 | 34 | 31 | 31 | 24* |
| Reactive | 265 | 198 | 73 | 40 | 32 | 25 | 17 | 15 | 11 | 8 | 8 | 7 | 6 | 5* |

Fig 2. Time to first relapse during the maintenance phase with proactive management or reactive management. Note: Patients who did not achieve PGA<2 after 4 weeks of once-daily rescue treatment after relapse were withdrawn from the trial but are included within this Kaplan-Meier curve. *30 patients in the proactive group vs 6 patients in the reactive group finished the trial without experiencing first relapse but had their final visit before day 364.

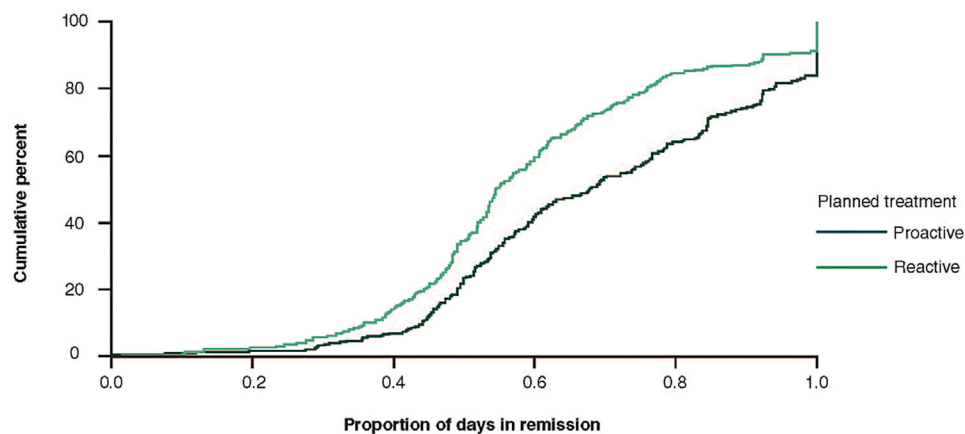


Fig 3. Cumulative proportion of days spent in remission during the maintenance phase with proactive management or reactive management.

changes or differences in serum or urinary calcium were observed between the treatment groups. Most patients' calcium levels remained stable over time. No clinically significant abnormalities in calcium metabolism or clinically relevant effect on calcium metabolism by subgroup analysis were observed.

In the HPA-axis subgroup (66 patients), 4 patients (2, proactive; 2, reactive) had a serum cortisol concentration $\leq 18 \mu\text{g/dL}$ 30 minutes after adrenocorticotrophic hormone challenge, and 1 patient in the

proactive group had a serum cortisol concentration $\leq 18 \mu\text{g/dL}$ 60 minutes after the adrenocorticotrophic hormone challenge. No patient had a serum concentration $\leq 18 \mu\text{g/dL}$ at both time points. Overall, no clinically relevant effect on the HPA-axis by subgroup analysis was observed.

The number of active treatment days during the maintenance phase was normalized by time of exposure. The proportion of active treatment days was 0.5 for patients in the proactive group vs 0.4 in

Table II. Adverse events during the open-label lead-in and maintenance phase

| AE category | Open-label lead-in phase (N = 650) | | Maintenance phase | | | |
|---------------------------|------------------------------------|-------------------|--------------------------------|-------------------|-------------------------------|-------------------|
| | AEs, No. | Patients, No. (%) | Proactive management (n = 272) | | Reactive management (n = 273) | |
| | | | AE, No. | Patients, No. (%) | AEs, No. | Patients, No. (%) |
| All AEs | 157 | 115 (17.7) | 303 | 133 (48.9) | 279 | 130 (47.6) |
| Serious AEs | 5 | 4 (0.6) | 15 | 14 (5.1) | 14 | 11 (4.0) |
| Treatment-related AEs* | 7 | 5 (0.8) | 5 | 5 (1.8) | 8 | 7 (2.6) |
| AEs leading to withdrawal | 2 | 2 (0.3) | 2 | 2 (0.7) | 1 | 1 (0.4) |
| Severe AEs | 1 | 1 (0.2) | 8 | 8 (2.9) | 15 | 14 (5.1) |
| Fatal AEs | 0 | 0 | 0 | 0 | 1 [†] | 1 (0.4) |

AEs, adverse events; No, number.

*Considered possibly or probably related to trial product by the investigator.

[†]The death was assessed as not related to trial product.

the reactive group. On average, the proactive group had 37.5 additional active treatment days per year vs the reactive group.

Local safety and tolerability of Cal/BD foam after relapse was favorable across all 4 parameters (redness, dryness, edema, erosion). Changes in pigmentation were not specified as part of the physician's assessment of local safety and tolerability; however, AEs of pigmentation disorder were reported by 1 patient in each group and considered possibly related to the trial product by the investigator.

DISCUSSION

Data on long-term management of psoriasis with topical treatments are needed. To date, no other study, to our knowledge, has reported on the long-term (up to 56 weeks) efficacy and safety of Cal/BD foam, and few studies have assessed longer-term efficacy and safety of Cal/BD ointment or gel.^{11,12}

Unlike other long-term studies that used intermittent (alternating between different active products) or on-demand regimens,^{11,12} this trial design allowed for comparison of Cal/BD foam with vehicle foam as a twice-weekly proactive maintenance regimen over 52 weeks for patients in remission. During a relapse, all patients received rescue treatment with Cal/BD foam once daily for 4 weeks. Consistent with previous 4-week data,¹³⁻¹⁵ Cal/BD foam was an effective rescue treatment: $\geq 75\%$ of patients achieved PGA "clear"/"almost clear" postrelapse during the maintenance phase.

Predicted mean number of relapses per year of exposure was reduced by more than one third in the proactive vs reactive group (3.1 vs 4.8) where patients received Cal/BD foam as rescue treatment. To achieve an additional 41 days in remission per year, longer time to first relapse, and fewer relapses overall, patients in the proactive group required

37.5 days of extra medication per year. In clinical practice, proactive management with Cal/BD foam might lead to fewer relapses and improved long-term disease control compared with conventional reactive treatment. Other parameters, such as patient preferences,¹⁶ may determine the most suitable patients for this regimen.

Overall, Cal/BD foam was well tolerated throughout the trial. The incidence of AEs during the 4-week open-label lead-in phase resembled other short-term studies with Cal/BD.^{13-15,17} The incidence of AEs in the maintenance phase was similar between treatment groups and similar to the incidence reported after treatment with Cal/BD foam once daily for 12 weeks.¹⁸ No new safety concerns were identified over 52 weeks.

This study has some limitations. As with other year-long studies,¹¹ statistical analysis was challenging because of the substantial but expected dropout rate (53.9%), which includes patients not achieving a PGA score "clear"/"almost clear" after rescue treatment. No clear association between BSA at baseline and dropout rates was observed (data not shown).

Rebound was defined as PASI $>125\%$ from baseline or when signs of more inflammatory disease appeared within 2 months of treatment discontinuation. This criterion was not optimal for patients with a low PASI, and several rebounds were classified only by numerical definition yet not as an AE of rebound.

CONCLUSION

Long-term proactive management over 52 weeks with fixed-dose Cal/BD foam twice-weekly was superior in prolonging time to the first relapse, reducing the number of relapses, and increasing days in remission compared with vehicle foam in adults with plaque psoriasis. Proactive management

with Cal/BD foam was well tolerated and had a favorable safety profile over the extended treatment period that was similar to reactive management where patients received Cal/BD foam as 4-week rescue treatment upon relapse only. No new AEs of interest were identified, including no clinical signs of skin atrophy. There was no clinically significant effect of Cal/BD foam on the HPA-axis or calcium metabolism. The results of this novel trial are very promising and suggest that proactive management with fixed-dose Cal/BD foam could offer improved long-term control of plaque psoriasis over conventional reactive treatment.

The authors thank the patients who participated in this trial and the PSO-LONG investigator group. The full list of investigators who participated in this trial in addition to the investigators listed as authors is available in the Supplemental material. The authors would like to acknowledge Stephanie Lacey, of Ashfield Healthcare Communications, part of UDG Healthcare plc, and Lauren Whyte, PhD, a freelance medical writer contracted by Ashfield Healthcare Communications, part of UDG Healthcare plc, for medical writing support that was funded by LEO Pharma in accordance with Good Publications Practice (GPP3) guidelines (<http://www.ismpp.org/gpp3>).

REFERENCES

1. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. *Lancet*. 2007;370(9583):263-271.
2. Chiu HY, Hui RC, Tsai TF, et al. Predictors of time to relapse following ustekinumab withdrawal in patients with psoriasis who had responded to therapy: an eight-year multicenter study. *J Am Acad Dermatol*. 2019. <https://doi.org/10.1016/j.jaad.2019.01.035>.
3. Gisondi P, Del Giglio M, Girolomoni G. Treatment approaches to moderate to severe psoriasis. *Int J Mol Sci*. 2017;18(2427):1-8.
4. Feldman SR, Goffe B, Rice G, et al. The challenge of managing psoriasis: unmet medical needs and stakeholder perspectives. *Am Health Drugs Benefits*. 2016;9(9):504-513.
5. Armstrong AW, Robertson AD, Wu J, et al. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003-2011. *JAMA Dermatol*. 2013;149(10):1180-1185.
6. Bonnekoh B, Fernández García JJ, Surber C, et al. Innovation that drives your dermatological future. *EMJ Dermatol*. 2017;5(1):36-43.
7. Wollenberg A, Bieber T. Proactive therapy of atopic dermatitis—an emerging concept. *Allergy*. 2009;64:276-278.
8. Wollenberg A, Reitamo S, Girolomoni G, et al. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. *Allergy*. 2008;63:742-750.
9. Electronic Medicines Compendium (emc). Enstilar Cutaneous Foam-Summary of Product Characteristics; 2019. Available at: <https://www.medicines.org.uk/emc/medicine/31833>. Accessed June 9, 2020.
10. U.S. Food and Drug Administration. Enstilar-Prescribing Information. 2019. Available at: https://www.accessdata.fda.gov/drugs_atfda_docs/label/2019/207589s005s006s007lbl.pdf. Accessed June 9, 2020.
11. Kragballe K, Austad J, Barnes L, et al. A 52-week randomized safety study of a calcipotriol/betamethasone dipropionate two-compound product (Dovobet/Daivobet/Taclonex) in the treatment of psoriasis vulgaris. *Br J Dermatol*. 2006;154(6):1155-1160.
12. Saraceno R, Camplone G, D'Agostino M, et al. Efficacy and maintenance strategies of two-compound formulation calcipotriol and betamethasone dipropionate gel (Xamiol® gel) in the treatment of scalp psoriasis: results from a study in 885 patients. *J Dermatolog Treat*. 2014;25(1):30-33.
13. Koo J, Tyring SM, Werschler WP, et al. Superior efficacy of calcipotriene and betamethasone dipropionate aerosol foam versus ointment in patients with psoriasis vulgaris—a randomized phase II study. *J Dermatolog Treat*. 2016;27(2):120-127.
14. Douglas WS, Poulin Y, Decroix J, et al. A new calcipotriol/betamethasone formulation with rapid onset of action was superior to monotherapy with betamethasone dipropionate or calcipotriol in psoriasis vulgaris. *Acta Derm Venereol*. 2002;82:131-135.
15. Papp KA, Guenther L, Boyden B, et al. Early onset of action and efficacy of a combination of calcipotriene and betamethasone dipropionate in the treatment of psoriasis. *J Am Acad Dermatol*. 2003;48(1):48-54.
16. Iversen L, Jakobsen HB. Patient preferences for topical psoriasis treatments are diverse and difficult to predict. *Dermatol Ther (Heidelb)*. 2016;6(2):273-285.
17. Taraska V, Tuppal R, Olesen M, et al. A novel aerosol foam formulation of calcipotriol and betamethasone has no impact on HPA axis and calcium homeostasis in patients with extensive psoriasis vulgaris. *J Cutan Med Surg*. 2016;20(1):44-51.
18. Paul C, Stein Gold L, Cambazard F, et al. Calcipotriol plus betamethasone dipropionate aerosol foam provides superior efficacy vs. gel in patients with psoriasis vulgaris: randomized, controlled PSO-ABLE study. *J Eur Acad Dermatol Venereol*. 2017;31:119-126.