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)

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Capsule summary [48/50 words]

- 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 versus vehicle foam for prolonging time to first relapse, increasing time in remission and reducing number of relapses.
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**Attachments:** CONSORT checklist; IRB approval letter; protocol and statistical analysis plan (for editor/reviewer reference only)
Key words: Psoriasis vulgaris; calcipotriene; betamethasone dipropionate; proactive; fixed-dose; topical preparation; foam; Enstilar; relapse; long-term; maintenance

Abbreviations: Cal/BD, fixed-dose combination calcipotriene 0.005%; betamethasone dipropionate 0.064%; BSA, body surface area; PGA, physician’s global assessment; m-PASI, modified psoriasis area and severity index; HPA, hypothalamic pituitary adrenal; AEs, adverse events; ICH, International Conference on Harmonisation; ANOVA, analysis of variance; FAS, full analysis set; SAS, safety analysis set; HR, hazard ratio; SD, standard deviation; CI, confidence interval; ACTH, adrenocorticotropic hormone;
Capsule summary [48/50 words]

- 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 versus vehicle foam for prolonging time to first relapse, increasing time in remission and reducing number of relapses.
Abstract [194/200 words, structured]

Background: Topical psoriasis treatment relies on a reactive, rather than 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 52-week, randomized, double-blind, maintenance phase. 545 patients achieved treatment success PGA ‘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: time to first relapse (PGA ≥‘mild’).

Results: 251 (46.1%) randomized patients completed the trial. Median time to first relapse: 56 days (proactive), 30 days (reactive). Patients in the proactive group had an additional 41 days in remission compared with the reactive group over 1 year ($P < 0.001$). Number of relapses per year of exposure: 3.1 (proactive), 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 versus reactive management.
INTRODUCTION

Psoriasis vulgaris is a chronic, relapsing inflammatory disease\(^1\) poorly categorized in terms of time to relapse in relation to treatment.\(^2,3\) Treatment involves topical agents in mild-to-moderate disease and as adjuncts to phototherapy, 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 as opposed to a proactive approach to maintain remission.\(^6\) Proactive therapy with calcineurin inhibitors in atopic dermatitis has been an emerging concept over the last decade\(^7\) 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\(^8\), LEO Pharma) is approved in the US (in adults and adolescents) and EU (in adults) for the treatment of psoriasis vulgaris for 4 weeks.\(^9\).

In this trial the efficacy and safety of long-term (52 weeks) twice-weekly proactive management with Cal/BD foam was compared with vehicle foam in the prevention of disease relapse in adults with psoriasis.
METHODS

Trial design and interventions

This phase III, multi-center 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). The trial was conducted at 56 participating sites in the United States, Canada, United Kingdom, France, Poland, and Germany.

Eligible patients: ≥18 years, with truncal and/or limb psoriasis, involving 2–30% of body surface area (BSA), physician’s global assessment of disease severity (PGA) score ≥‘mild’ (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 4–16 weeks (depending on therapy); and systemic treatment with other therapies with a possible effect on psoriasis within 4 weeks, prior to baseline. A subgroup of these patients with 10–30% BSA and PGA ≥‘moderate’ (PGA≥3) underwent hypothalamic pituitary adrenal (HPA)-axis testing at baseline, randomization, 28 weeks and 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 and/or limbs for 4 weeks. The purpose of this phase was to select responders to treatment. Treatment success was defined as a PGA score ‘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’). 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 PGA score ‘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 following the end of treatment/early withdrawal. Rebound was defined as an m-PASI ≥12 and an increase in m-PASI ≥125% of the baseline value, or the development of new pustular, erythrodermic, more inflammatory psoriasis within 2 months of treatment discontinuation in either the open-label lead-in phase, after discontinuation of once-daily rescue medication, or following the end of maintenance phase.

See supplementary information for further details on trial design, interventions and changes to planned analyses.

**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 safety of long-term proactive management.

Endpoints

Primary endpoint: time to first relapse (PGA score ≥‘mild’). Secondary endpoints: proportion of days in remission (PGA score ‘clear’/‘almost clear’); number of relapses. Exploratory endpoints: 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); 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.\textsuperscript{11} It was assumed that this would be the case in this trial and that between 4–8 relapses would occur per year in the vehicle group. A 30% reduction in a hazard, i.e., a hazard ratio of 0.7, for the proactive group relative to reactive group was considered of clinical interest. Based on a two-sample survival test, 380 patients were planned to be randomized to obtain a power of 90% for a 5% significance level. Per the trial protocol and to comply with International Council for Harmonisation's (ICH) E1 regarding long-term safety, more patients were recruited and randomized to compensate for the dropout rate.\textsuperscript{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. Proportion of days in remission was analyzed by
an analysis of variance (ANOVA) 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 subjects. Predicted number of relapses
was analyzed in a Poisson regression model with treatment group, pooled sites,
disease severity at maintenance baseline as factors, subject as 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 and/or Independent Ethics Committees and Regulatory Authorities,
for each participating site, prior to 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

Six-hundred and fifty patients entered the open-label lead-in phase, of which 521 (80.2%) achieved treatment success at Week 4 and were randomized in the maintenance phase (full analysis set [FAS]: proactive, n = 256; reactive, n = 265).

Twenty-four 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). Two-hundred and fifty-one (46.1%) randomized patients completed the 52-week maintenance period (Fig 1).

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

Efficacy

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 (± SD) and BSA (± SD) in patients achieving treatment success during the open-label lead-in phase and included in the SAS was −81.1% (17.9%) and −55.7% (38.2%), respectively.
During the maintenance phase, the estimated median time to first relapse from randomization 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 first relapse was reduced by 43% in the proactive versus reactive management group (HR, 0.57; 95% confidence interval [CI], 0.47, 0.69; \( P < 0.001 \)).

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 versus reactive group; estimated treatment difference 11% (95% CI, 8, 14%; \( P < 0.001 \)), corresponding to 41 extra days in remission over 1 year (Fig 3). The rate of relapse was 46% lower (95% CI, 37, 54%; \( P < 0.001 \)) in the proactive group versus the reactive group. The predicted number of relapses per year of exposure was 3.1 (proactive) versus 4.8 (reactive).

Both groups responded to rescue treatment with Cal/BD foam, with the majority of patients achieving PGA ‘clear’/‘almost clear’ (overall response: 75.9% and 81.0% in the proactive and reactive groups, respectively). Patients failing to achieve treatment success following rescue treatment were withdrawn from the study (\( n = 65 \) and \( n = 70 \) for patients in the proactive and reactive groups, respectively), (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 and 158.4 in the proactive and reactive groups, respectively. 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 were considered not related to 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 one patient in the reactive management group had an AE of pruritus. Three patients (2 proactive and 1 reactive) had non-serious AEs that were adjudicated as related to long-term corticosteroid use (see supplementary information for further details).

The number of rebounds within 2 months of entering the maintenance phase were 6 and 7 in the proactive and reactive groups, respectively. Following 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 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 ≤18 µg/dL 30 minutes after adrenocorticotropic hormone (ACTH) challenge and 1 patient in the proactive group had a serum cortisol concentration ≤18 µg/dL 60 minutes after ACTH challenge. No patient had a serum concentration ≤18 µg/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 versus 0.4 in the reactive group. On average, the proactive group had 37.5 additional active treatment days per year versus the reactive group.

Local safety and tolerability of Cal/BD foam following a 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 trial product by the investigator.
DISCUSSION

Data on long-term management of psoriasis with topical treatments are needed. To date, no other study 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 either 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; ≥75% of patients achieved PGA ‘clear’/‘almost clear’ post-relapse during the maintenance phase.

Predicted mean number of relapses per year of exposure was reduced by more than a third in the proactive versus 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 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 preferences¹⁶ 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
The incidence of AEs in the maintenance phase was similar between treatment groups and similar to the incidence reported following treatment with Cal/BD foam once-daily for 12 weeks. No new safety concerns were identified over 52 weeks.

**Limitations**

As with other year-long studies, 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’ following rescue treatment. No clear association between BSA at baseline and dropout rates were 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 criteria was not optimal for patients with low PASI, and several rebounds were classified only by numerical definition yet not as an AE of rebound.
CONCLUSIONS

Long-term proactive management over 52 weeks with fixed-dose Cal/BD foam twice-weekly was superior in prolonging time to first relapse, reducing 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.
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REFERENCES


### Table I. Baseline characteristics

<table>
<thead>
<tr>
<th>Demographics and disease characteristics at baseline</th>
<th>All patients assigned to treatment in open-label lead-in phase</th>
<th>Patients randomized in the maintenance phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 650</td>
<td>Proactive n = 272</td>
<td>Reactive n = 273</td>
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</table>

#### Sex
- Female n, (%) 226 (34.8) 86 (31.6) 87 (31.9)
- Male n, (%) 424 (65.2) 186 (68.4) 186 (68.1)

#### Age
- Mean (SD) 51.8 (14.2) 52.5 (14.9) 52.0 (13.7)
- Min; Max 19.0; 84.0 19.0; 84.0 19.0; 84.0

#### BMI (kg/m²)
- Mean (SD) 29.5 (6.6) 29.1 (6.0) 29.5 (6.8)
- Min; Max 16.1; 64.8 17.1; 50.5 16.1; 64.8

#### Race†
- White n, (%) 584 (92.0) 238 (89.8) 249 (92.9)
- Asian n, (%) 37 (5.8) 22 (8.3) 13 (4.9)
- Black or African American n, (%) 9 (1.4) 3 (1.1) 4 (1.5)
- Other n, (%) 5 (0.8) 2 (0.8) 2 (0.7)

#### Duration of psoriasis
- Mean (SD) 18.4 (13.7) 18.8 (13.3) 18.1 (13.9)‡
- Min; Max 1.0; 74.0 1.0; 62.0 1.0; 74.0

#### PGA
- Mild n, (%) 83 (12.8) 25 (9.2) 33 (12.1)
- Moderate n, (%) 509 (78.3) 223 (62.0) 224 (62.1)
- Severe n, (%) 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)
- Min; Max 2.0; 32.4 2.0; 28.0 2.0; 19.2

#### BSA (%)
- Mean (SD) 8.2 (6.4) 8.4 (6.4) 8.1 (6.3)
- Min; Max 1.0; 38.0 1.0; 36.0 2.0; 38.0

*All baseline characteristics for all analysis groups were collected at baseline of the open-label lead-in phase, prior to treatment with Cal/BD foam.
†Patients, n = 635; Ca/BD, n = 265; vehicle, n = 268.

‡Patients, n = 272.

BSA, body surface area; BMI, body mass index; m-PASI, modified psoriasis severity index score;
PGA, physician’s global assessment; SD, standard deviation.
Table II. Adverse events during the open-label lead-in and maintenance phase

<table>
<thead>
<tr>
<th>AE category</th>
<th>Open-label lead-in phase n = 650</th>
<th>Maintenance phase</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number of AEs</td>
<td>Number of patients (%)</td>
</tr>
<tr>
<td>All AEs</td>
<td>157</td>
<td>115 (17.7)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>5</td>
<td>4 (0.6)</td>
</tr>
<tr>
<td>Treatment-related AEs*</td>
<td>7</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td>AEs leading to withdrawal</td>
<td>2</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Severe AEs</td>
<td>1</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Fatal AEs</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Considered possibly or probably related to trial product by the investigator.
†The death was assessed as not related to trial product.

AEs, adverse events.
Figure legends

Figure 1. Psoriasis. Trial design and patient disposition (CONSORT diagram).

1 All patients received Cal/BD foam once-daily for 4 weeks during the open-label lead-in phase.
2 Treatment success was defined as a physician’s global assessment of disease severity (PGA) score ‘clear’/‘almost clear’ with ≥2-grade improvement from baseline.
3 Excluded from FAS.
4 If 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. Following 4 weeks of once-daily rescue treatment, patients who regained PGA<2 (‘clear’/’almost clear’) re-started the twice-weekly maintenance treatment according to the original randomization scheme. Patients who did not regain a PGA score <2 (‘clear’/’almost clear’) following 4 weeks of once-daily rescue medication were withdrawn from the trial.
5 Rebound was defined as an m-PASI ≥12 and an increase in m-PASI ≥125% of the baseline value of the open-label phase, or the development of new pustular, erythrodermic, more inflammatory psoriasis within two months of entering the maintenance phase, within 2 months after a previous relapse or within 2 months after the end of the maintenance phase.

FAS, full analysis set; m-PASI, modified psoriasis severity index score; PGA, physician’s global assessment; SAS, safety analysis set.

Figure 2. Psoriasis. 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 following 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 prior to Day 364.

Figure 3. Psoriasis. Cumulative proportion of days spent in remission during the maintenance phase with proactive management or reactive management.
The graph illustrates the probability of having not had a relapse yet for different treatment groups over days after randomization. The treatment groups are denoted as Proactive and Reactive.

- **Proactive Group**
  - Days 1, 28, 56, 84, 112, 140, 168, 196, 224, 252, 280: 1.00, 0.75, 0.50, 0.25, 0.10, 0.05, 0.00, 0.00, 0.00, 0.00
  - Number of patients at risk of relapse:
    - Days 1 to 364, Proactive: 256, 219, 128, 100, 83, 75, 65, 47, 41, 36, 34, 31, 31, 24

- **Reactive Group**
  - Days 1, 28, 56, 84, 112, 140, 168, 196, 224, 252, 280: 1.00, 0.75, 0.50, 0.25, 0.10, 0.05, 0.00, 0.00, 0.00, 0.00
  - Number of patients at risk of relapse:
    - Days 1 to 364, Reactive: 265, 198, 73, 40, 32, 25, 17, 15, 11, 8, 8, 7, 6, 5

*Note: The asterisk (*) indicates the last reported data point for each group.*
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