Safety of long-term proactive management with fixed-dose combination calcipotriene 0.005% and betamethasone dipropionate 0.064% foam in patients with psoriasis vulgaris: results of a Phase III, multicentre, 52-week, vehicle-controlled trial

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Introduction
- Topical therapies are considered first-line treatment for psoriasis, but however maintaining long-term disease control is a challenge, with many patients untreated or undertreated. Current topical psoriasis treatment relies on a reactive approach to disease flares, as opposed to a more long-term proactive approach.
- Data supporting the efficacy and safety of calcipotriene 0.005% and betamethasone dipropionate 0.064% (Cal/BD) foam approved as a reactive treatment are available from trials of 4- and 12-weeks duration in patients with psoriasis vulgaris (plaque psoriasis).
- Here, we report the safety of Cal/BD foam for the long-term proactive management of psoriasis over 52 weeks (NCT020899662).

Materials and Methods
- This Phase III, multicenter trial included a 4-week open-label lead-in phase in adult patients with:
  - Trunk and/or limb psoriasis, involving 2-30% of body surface area (BSA); physician’s global assessment (PGA) of disease severity >2 mild modified psoriasis area and severity index (m-PASI) 32.
- Following the open-label lead-in phase, patients with treatment success (PGA score of ‘clear’ or ‘almost clear’ (PGA=0) or at least 2-grade improvement from baseline) were randomized to the 52-week double-blind, vehicle-controlled maintenance phase.
- The trial included a subgroup of patients at assigned sites who underwent hypothalamic pituitary adrenal (HPA) testing.

Double-blind trial
- ‘Proactive’ management was treatment with Cal/BD foam twice-weekly for 52 weeks when in remission.
- ‘Reactive’ management was treatment with vehicle foam twice-weekly for 52 weeks when in remission.
- Relapse: PGA≥2 (either previously treated and/or new skin area). Flare medication (as separate flare bottles) was Cal/BD foam once daily for 4 weeks for both the proactive and reactive management groups (Figures 1).

Primary objective
- Efficacy objectives, endpoints and data are presented in posterior #18223.

Table 1. Overview of AEs

<table>
<thead>
<tr>
<th>AE category</th>
<th>Number of AEs</th>
<th>Number (%) of patients</th>
<th>Number of AEs</th>
<th>Number (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEs</td>
<td>333</td>
<td>136 (40.9)</td>
<td>279</td>
<td>132 (47.5)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>15</td>
<td>14 (4.1)</td>
<td>14</td>
<td>11 (4.0)</td>
</tr>
<tr>
<td>Treatment-related AEs</td>
<td>5</td>
<td>5 (1.8)</td>
<td>7</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>AE leading to withdrawal</td>
<td>2 (0.7)</td>
<td>1 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe AEs</td>
<td>8</td>
<td>8 (2.9)</td>
<td>15</td>
<td>14 (4.8)</td>
</tr>
</tbody>
</table>

Safety objectives and endpoints
- To evaluate the long-term safety of proactive management with Cal/BD foam (up to 52 weeks) in patients with psoriasis. Safety endpoints included:
  - Adverse events (AEs) associated with long-term corticosteroid use.
  - Incidence of rebound (see Table 3 for definition).
  - Effect on calcium metabolism based on serum/urinary calcium. Effect on HPA-axis based on serum cortisol.

Results
- 545 patients were randomized (safety analysis set [SAS]; proactive management with Cal/BD foam [N=272]; reactive management with Cal/BD foam [N=273]). 251 (46.1%) patients completed the trial. Mean age was 52.2 ± 17.9 years; 91% patients were white and 68% were male.
- AE adjudicated as associated with long-term corticosteroid use in maintenance phase
  - Cholestasis in one patient: severe intensity, onset on Day 31, considered related to treatment by investigator, no led to withdrawal of treatment [proactive].
  - Pain of skin in one patient: moderate intensity, onset on Day 310, considered possibly related to treatment by investigator, no action taken with treatment [proactive].

AEs adjudicated as associated with long-term corticosteroid use in maintenance phase
- AEs reported in >5% of patients: nasopharyngitis (8.1% proactive vs. 7.0% reactive) and upper respiratory tract infection (5.9% vs. 5.2%); all were considered related to treatment by the investigator.

AEs associated with long-term corticosteroid use in maintenance phase
- No consistent changes or differences in serum or urinary calcium between the two treatment groups.
- No clinically significant abnormalities in calcium metabolism were observed.
- In the HPA-axis group, no patient had serum cortisol ≤18 µg/dL at any timepoint.

Conclusions
- Proactive management with Cal/BD foam was well tolerated, with a favorable safety profile over the extended treatment period that was similar to the vehicle-controlled reactive treatment group.
- Proactive management with Cal/BD foam had no clinically significant effects on the HPA-axis or calcium metabolism.

Other safety results
- No consistent changes or differences in serum or urinary calcium between the two treatment groups.
- No clinically significant abnormalities in calcium metabolism were observed.
- In the HPA-axis group, no patient had serum cortisol ≤18 µg/dL at any timepoint.

References

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Disclosures
- All authors report no conflict of interest in connection with the present study. All authors contributed to the writing and critical review of the manuscript. All authors had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

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