The Safety and Efficacy of Roflumilast Cream 0.15% and 0.05% in Atopic Dermatitis: Phase 2 Proof-of-Concept Study

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Disclosures

M.J. Gooderham has been a speaker, advisory board member, investigator and/or consultant for AbbVie, Akros, Amgen, Arcutis, BMS, Boehringer Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly, Galderma, GSK, Incyte, Janssen, Kyowa Kirin, LEO Pharma, Medimmune, Merck, Novartis, Pfizer, Regeneron, Sanofi Genzyme, UCB Pharma, and Valeant/Bausch.


M. Zirwas is an investigator, consultant, and/or speaker for AbbVie, Arcutis, Asana, Avillion, Dermavant, DS Biopharma, Edessa Biotech, Fit Bit, Foamix, Galderma, Genentech/Novartis, Incyte, Janssen, Leo Pharma, L’Oreal, Lilly, Menlo, Ortho Derm, Pfizer, Regeneron/Sanoﬁ, and UCB Pharma, and is part owner of AsepticMD. M. Lee is an investigator for AbbVie, Arcutis, Bausch Health, Boehringer Ingelheim, Dermavant, Dermira, Eli Lilly, Incyte, Foamix, Pfizer, and UCB. S.E. Kempers is an investigator for Arcutis, and serves as a consultant for Foamix and Kinex.

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Majority of patients with atopic dermatitis are treated with topical anti-inflammatory therapy: corticosteroids or calcineurin inhibitors, in combination with emollients. Side effects and poor adherence limit long-term use of topical corticosteroids. Topical calcineurin inhibitors may cause local tolerability reactions.

PDE-4 is the predominant cAMP-degrading enzyme in inflammatory cells, including lymphocyte subsets, and has increased activity in inflammatory skin disorders like atopic dermatitis.

Roflumilast cream is a highly potent PDE-4 inhibitor with ~25- to >300-fold higher potency than other approved PDE-4 inhibitors.

The objective of this study was to assess the short-term safety and efficacy of QD topical roflumilast cream in patients with mild to moderate atopic dermatitis.
The Safety and Efficacy of Roflumilast Cream in Atopic Dermatitis: Study Design

**Randomized, double-blind, vehicle-controlled, multicenter study**

**ELIGIBILITY**
- Mild or moderate atopic dermatitis (vIGA-AD=2 or 3)
- Age ≥12 years
- 1.5-35% BSA
- EASI >5

**Randomization**
- 1:1:1

**N=136**

**ENDPOINTS**
- **Primary:** EASI change from baseline
- **Secondary:**
  - EASI % change from baseline
  - EASI-50 and EASI-75
  - BSA
  - WI-NRS
- **Exploratory:**
  - vIGA-AD *clear/almost* clear
  - vIGA-AD *clear/almost* clear + ≥2-grade improvement
- **Safety and tolerability**

**Roflumilast cream 0.15% QD**

**Roflumilast cream 0.05% QD**

**Vehicle QD**

*The primary endpoint was analyzed with a mixed-effects model for repeated measures, as were other continuous endpoints. Categorical endpoints were analyzed with a Cochran-Mantel-Haenszel (CMH) test. Comparisons were specified at the 0.05 level and were not adjusted for multiplicity. BSA: body surface area; EASI: Eczema Area and Severity Index; QD: once daily; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis; WI-NRS: Worst Itch Numeric Rating Scale.*

PRESENTED AT THE 29TH EUROPEAN ACADEMY OF DERMATOLOGY AND VENEREOLOGY CONGRESS, EADVIRTUAL, OCTOBER 29-31, 2020
### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Roflumilast 0.15% (n=45)</th>
<th>Roflumilast 0.05% (n=46)</th>
<th>Vehicle (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (SD)</td>
<td>38.0 (16.5)</td>
<td>44.3 (17.0)</td>
<td>42.4 (17.6)</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>33 (73.3)</td>
<td>31 (67.4)</td>
<td>29 (64.4)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>24 (53.3)</td>
<td>32 (69.6)</td>
<td>32 (71.1)</td>
</tr>
<tr>
<td>Black</td>
<td>14 (31.1)</td>
<td>11 (23.9)</td>
<td>11 (24.4)</td>
</tr>
<tr>
<td>Multiple/other</td>
<td>7 (15.6)</td>
<td>3 (6.5)</td>
<td>2 (4.4)</td>
</tr>
<tr>
<td>vIGA-AD score, mean (SD)</td>
<td>2.8 (0.4)</td>
<td>2.8 (0.4)</td>
<td>2.8 (0.4)</td>
</tr>
<tr>
<td>2 (mild), n (%)</td>
<td>10 (22.2)</td>
<td>11 (23.9)</td>
<td>9 (20.0)</td>
</tr>
<tr>
<td>3 (moderate), n (%)</td>
<td>35 (77.8)</td>
<td>35 (76.1)</td>
<td>36 (80.0)</td>
</tr>
<tr>
<td>EASI, mean score (SD)</td>
<td>9.5 (4.1)</td>
<td>8.4 (4.1)</td>
<td>9.2 (3.9)</td>
</tr>
<tr>
<td>BSA, mean (SD), %</td>
<td>9.6 (6.0)</td>
<td>8.4 (7.1)</td>
<td>10.5 (6.6)</td>
</tr>
<tr>
<td>WI-NRS, mean score (SD)</td>
<td>6.6 (2.0)</td>
<td>6.5 (2.0)</td>
<td>7.2 (2.1)</td>
</tr>
<tr>
<td>WI-NRS score ≥6, n (%)</td>
<td>32 (71.1)</td>
<td>31 (67.4)</td>
<td>38 (84.4)</td>
</tr>
</tbody>
</table>

Data are presented for safety population. BSA: body surface area; EASI: Eczema Area and Severity Index; SD: standard deviation; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis; WI-NRS: Worst Itch Numeric Rating Scale.
Severity of Atopic Dermatitis Improved With Roflumilast Cream

At this early timepoint of 4 weeks, there was improvement in atopic dermatitis severity, yet not statistically significant.

A robust response to vehicle was observed.

Data presented for intent-to-treat population. CI: confidence interval; EASI: Eczema Area and Severity Index; LS: least squares.
Secondary and Exploratory Endpoints Showed Significant Improvement With Roflumilast Cream Over Vehicle

Data presented for intent-to-treat population. Only significant P-values (P<0.05) shown. CI: confidence interval; EASI: Eczema Area and Severity Index; LS: least squares; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis.
Efficacy of Roflumilast Cream Continued to Improve Through Week 4

Data presented for intent-to-treat population. Only significant P-values (P<0.05) shown. CI: confidence interval; EASI: Eczema Area and Severity Index; LS: least squares; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis.
Roflumilast Cream Improved Severity of Atopic Dermatitis

**Roflumilast 0.15%**

**Vehicle**

**Baseline**

**Week 4**

vIGA-AD = 3

vIGA-AD = 3

EASI CFB = -77%

EASI CFB = -27%

CFB: change from baseline; EASI: Eczema Area and Severity Index; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis.
TEAEs Uncommon; Similar Incidence Across Groups

- Safety and tolerability of roflumilast was similar to vehicle group
- All TEAEs were mild or moderate
- Low rates of application site AEs
- No psychiatric TEAEs
- No unintentional weight loss of more than 5%

<table>
<thead>
<tr>
<th>Category, n (%)</th>
<th>Roflumilast 0.15% (n=45)</th>
<th>Roflumilast 0.05% (n=46)</th>
<th>Vehicle (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any TEAE</td>
<td>12 (26.7)</td>
<td>10 (21.7)</td>
<td>6 (13.3)</td>
</tr>
<tr>
<td>Any treatment-related TEAE</td>
<td>0</td>
<td>2 (4.3)</td>
<td>2 (4.4)</td>
</tr>
<tr>
<td>TEAE leading to study discontinuation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>1 (2.2)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>SAE&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td>1 (2.2)</td>
<td>0</td>
</tr>
<tr>
<td>Maximum severity of TEAEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>10 (22.2)</td>
<td>6 (13.0)</td>
<td>5 (11.1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 (4.4)</td>
<td>4 (8.7)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Application site TEAEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Application site pain</td>
<td>0</td>
<td>1 (2.2)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Atopic dermatitis worsening</td>
<td>0</td>
<td>0</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Skin laceration&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0</td>
<td>1 (2.2)</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Roflumilast 0.05%: moderate application site pain; vehicle: moderate worsening of AD. <sup>b</sup>Roflumilast 0.03%: mild traumatic spinal cord compression that was considered unrelated to the study drug. <sup>c</sup>Unrelated to the study drug.

Data presented for safety population. AE: adverse event; AEd: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

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Conclusions

• In this small proof-of-concept study, once-daily roflumilast cream demonstrated efficacy compared with vehicle cream in atopic dermatitis
  – Primary endpoint showed a trend towards, but did not reach, statistical significance
  – Statistical significance was reached for other efficacy endpoints
  – Substantial efficacy noted, with 72.3% EASI improvement and >50% of patients achieving clear or almost clear skin on vIGA-AD at Week 4 for roflumilast cream 0.15%
  – Continued efficacy through Week 4
  – High response rate with cream vehicle in this study may have been a factor in not reaching statistical significance in the primary endpoint
• Roflumilast cream was well-tolerated, with a low rate of application site reactions, and no signs of local irritation

**Roflumilast cream**, a potent PDE-4 inhibitor, represents a potential effective QD topical treatment for atopic dermatitis. Favorable safety profile and encouraging efficacy results warrant further investigation of roflumilast cream in larger studies over longer times
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