Direct and Indirect Effects of Crisaborole Ointment on Quality of Life in Patients With Atopic Dermatitis: A Mediation Analysis

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BACKGROUND
- Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by intensely pruritic eczematous lesions.1
- Itch has a significant impact on quality of life (QoL) in children and adults, and it is one of the most important aspects of the disease that patients use to judge treatment response.2-4
- Contactant and calcineurin inhibitors are recommended for topical treatment of AD;5 however, there is a need for new, effective, nonsteroidal treatments that address inflammation and itch without the potential limitations associated with current topical agents.
- Crisaborole ointment is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild to moderate AD.6
- In 2 identically designed Phase 3 clinical studies (AD-301: NCT02118766; AD-302: NCT02118752), crisaborole ointment, 2%, significantly improved global disease severity and all measured signs and symptoms of AD, and did not result in any treatment-related serious treatment-emergent adverse events.7
- The most common treatment-related adverse event was application site pain (pooled AD-301 and AD-302 population: crisaborole: 4.4%, vehicle: 1.2%).
- Mediation modeling has been used to establish the contributions of direct and indirect effects of a treatment on an outcome.8-10

OBJECTIVES
- Through mediation modeling, determine the interrelationship among patient-reported pruritus (as measured by SPS), QoL, as measured by the Dermatology Life Quality Index (DLQI) or the Children’s Dermatology Life Quality Index (CDLQI), and treatment using pooled data from AD-301 and AD-302.

METHODS
Study Treatment
- In the Phase 3 studies, patients aged 2 years or younger were randomly assigned in a 2:1 ratio to receive crisaborole or vehicle ointment.
- Treatment was applied twice daily for 28 days.
- QoL was measured using the DLQI in patients aged ≥16 years and the CDLQI in patients aged 2-15 years (Table 1).11,12

Table 1. QoL Assessment Scales and Subcales: CDLQI and DLQI

<table>
<thead>
<tr>
<th>Category</th>
<th>CDLQI Patients Aged 2-15 Years</th>
<th>CDLQI Patients Aged ≥16 Years</th>
<th>DLQI Patients Aged 2-15 Years</th>
<th>DLQI Patients Aged ≥16 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom &amp; Feelings</td>
<td>0-3 pts</td>
<td>0-3 pts</td>
<td>0-3 pts</td>
<td>0-3 pts</td>
</tr>
<tr>
<td>Personal Relationships</td>
<td>0-4 pts</td>
<td>NA</td>
<td>0-4 pts</td>
<td>NA</td>
</tr>
<tr>
<td>School/Work &amp; Holidays</td>
<td>0-3 pts</td>
<td>0-3 pts</td>
<td>0-3 pts</td>
<td>0-3 pts</td>
</tr>
<tr>
<td>Leukus</td>
<td>0-4 pts</td>
<td>0-4 pts</td>
<td>0-4 pts</td>
<td>0-4 pts</td>
</tr>
<tr>
<td>Burden of Treatment</td>
<td>0-3 pts</td>
<td>0-3 pts</td>
<td>0-3 pts</td>
<td>0-3 pts</td>
</tr>
<tr>
<td>Effect of skin on sleep</td>
<td>0-3 pts</td>
<td>0-3 pts</td>
<td>0-3 pts</td>
<td>0-3 pts</td>
</tr>
<tr>
<td>Daily Activities</td>
<td>0-4 pts</td>
<td>NA</td>
<td>0-4 pts</td>
<td>NA</td>
</tr>
<tr>
<td>Total</td>
<td>0-30 pts</td>
<td>0-30 pts</td>
<td>0-30 pts</td>
<td>0-30 pts</td>
</tr>
</tbody>
</table>

RESULTS
Patients Demographics and Disposition
- Between both studies, 1016 patients were randomly assigned to receive crisaborole and 506 patients were randomly assigned to receive vehicle (intent-to-treat population).
- Baseline demographics and disease characteristics were balanced between the treatment arms.
- The mean age of both groups was approximately 12.2 years; most patients (88%) were 2-17 years of age.
- Approximately 55.6% were female; most (80%) were non-Hispanic.
- Between both groups, distribution by race was approximately 61%, white (≥98.5%) were 2-17 years of age.
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Baseline disease characteristics are summarized in Table 3.13

Table 3. Baseline Disease Characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Crisaborole n=1016</th>
<th>Vehicle n=506</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGA, n (%)</td>
<td>393 (38.7)</td>
<td>393 (39.1)</td>
</tr>
<tr>
<td>Severe/Extreme: %</td>
<td>19 (1.9)</td>
<td>19 (1.9)</td>
</tr>
<tr>
<td>Moderate: %</td>
<td>331 (32.8)</td>
<td>331 (33.5)</td>
</tr>
<tr>
<td>Moderate/Severe: %</td>
<td>136 (13.4)</td>
<td>136 (13.9)</td>
</tr>
<tr>
<td>Treatable % BSA</td>
<td>18.1 (10.9)</td>
<td>18.1 (17.5)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5.95</td>
<td>5.90</td>
</tr>
<tr>
<td>Total</td>
<td>9 (3.2)</td>
<td>9 (3.0)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>102</td>
<td>102</td>
</tr>
</tbody>
</table>

REFERENCES

CONCLUSIONS
- Mediation modeling can be used to help explain the effect of a treatment on an outcome.
- The presented mediation models indicate that crisaborole affects QoL mostly indirectly through improvement in the severity of pruritus.
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