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Tapinarof: Therapeutic AhR Modulating Agent (TAMA)

- Tapinarof is a topical, small molecule TAMA that directly binds to and activates AhR transcription factor\(^1\)
- AhR activation via tapinarof *in vitro* and animal models leads to:
  - Reduction of Th17 cytokine expression\(^1\)
  - Reduction of Th2 cytokine expression\(^1,2\)
  - Decreased oxidative stress\(^1\)
  - Increased skin barrier proteins\(^1\)

AhR pathway\(^3\)

AhR, aryl hydrocarbon receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; TAMA, therapeutic aryl hydrocarbon receptor modulating agent; Th, T helper cell.

Tapinarof Cream 1% QD for the Treatment of Plaque Psoriasis: Efficacy and Safety in Two Pivotal Phase 3 Trials

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Tapinarof 1% QD: Primary Endpoint of PGA Response at Week 12 was Achieved in Both Studies

PGA response rate* was highly statistically significant in the tapinarof cream 1% QD group versus vehicle in both PSOARING 1 and 2: 35.4% vs 6.0% (P<0.0001) and 40.2% vs 6.3% (P<0.0001), respectively

*PGA of 0 or 1 and ≥2-grade improvement at Week 12.
ITT population. P value based upon Cochran-Mantel-Haenszel analysis stratified by baseline PGA score.
ITT, intent-to-treat; PGA, Physician Global Assessment; QD, once daily; SEM, standard error of mean
Tapinarof 1% QD Clinical Response of Patient with Plaque Psoriasis who Achieved Primary and Secondary Efficacy Endpoints at Week 12

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGA</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PASI</td>
<td>17.6</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

PGA and PASI are global efficacy assessments. Example of one representative target lesion of a patient treated with tapinarof 1% QD; individual results may vary. Photographs demonstrate improvement in PGA and PASI at Week 4 and 12. PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; QD, once daily.
Tapinarof 1% QD AE Profile Consistent with Previous Studies\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>PSOARING 1</th>
<th>PSOARING 2</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Tapinarof 1% QD (n=340)</td>
<td>Vehicle QD (n=170)</td>
</tr>
<tr>
<td>Most common treatment-related TEAEs (≥1% in any group)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folliculitis</td>
<td>70 (20.6)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>13 (3.8)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (1.5)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (1.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>1 (0.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Study discontinuation due to AESI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folliculitis</td>
<td>6 (1.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>5 (1.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Severity of folliculitis, n (%) among subset of patients with AESI of folliculitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1 (63.8)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>Moderate</td>
<td>3 (35.0)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (1.3)</td>
<td>0 (0.0)</td>
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- The most common (≥1% in any group) treatment-related TEAEs were folliculitis, contact dermatitis, headache, pruritus, and dermatitis.
- Folliculitis was mostly mild or moderate in severity in both studies and study discontinuation due to folliculitis was low: 1.8% (6/340) vs 0.0% (0/170) and 0.9% (3/343) vs 0.0% (0/172) in PSOARING 1 and 2, respectively.

A patient is counted once only for each MedDRA preferred term. Safety population. TEAE defined as an AE that starts on or after the date of first dose of study drug.
AE, adverse event; AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; QD, once daily; TEAE, treatment-emergent adverse event.
Biologic Effects of Tapinarof

- Tapinarof is a small molecule therapeutic AhR modulating agent (TAMA) that uniquely activates the AhR pathway to decrease pro-inflammatory cytokines, decrease oxidative stress, increase skin barrier proteins and re-establish skin homeostasis\(^1\)

\[\text{AhR} \rightarrow \text{Tapinarof} \rightarrow \text{Th17 cytokines}^{*+1} \rightarrow \text{Inflammation in psoriasis}\]

\[\text{AhR} \rightarrow \text{Filaggrin, loricrin, and involucrin}^{*1,2} \rightarrow \text{Skin barrier repair}\]

\[\text{AhR} \rightarrow \text{Th2 cytokines}^{*4,5} \rightarrow \text{Inflammation in atopic dermatitis}\]

\[\text{AhR} \rightarrow \text{Antioxidant activity via Nrf2 pathway}^{*+1-3} \rightarrow \text{Oxidative Stress}\]

\(\text{C}_{17}\text{H}_{13}\text{O}_2\) \ MW: 254 g/mol

\(\text{Th17 cytokines}^{*+1}\)

\(\text{Inflammation in psoriasis}\)

\(\text{Filaggrin, loricrin, and involucrin}^{*1,2}\)

\(\text{Skin barrier repair}\)

\(\text{Th2 cytokines}^{*4,5}\)

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Roflumilast cream (ARQ-151) is a potent, selective PDE-4 inhibitor. Demonstrates ~25- to >300-fold higher potency than currently available PDE-4 inhibitors.

ARQ-151, Roflumilast Cream, Improved Chronic Plaque Psoriasis in Phase 2b Study

Mark G. Lebwohl¹, Kim A. Papp², Linda Stein Gold³, Melinda J. Gooderham⁴, Leon H. Kircik⁵, Zoe D. Draelos⁶, Steven E. Kempers⁷, Mathew Zirwas⁸, Kathleen Smith⁹, David W. Osborne⁹, Marie-Louise Trotman¹⁰, Lynn Navale⁹, Charlotte Merritt⁹, David R. Berk⁹, Howard Welgus⁹

¹Icahn School of Medicine at Mount Sinai, New York, NY, USA; ²Probity Medical Research and K Papp Clinical Research, Waterloo, ON, Canada; ³Henry Ford Medical Center, Detroit, MI, USA; ⁴Skin Centre for Dermatology, Probity Medical Research and Queen's University, Peterborough, ON, Canada; ⁵Icahn School of Medicine, Mount Sinai, New York, NY, and Skin Sciences, Louisville, KY, USA; ⁶Dermatology Consulting Services, High Point, NC, USA; ⁷Minnesota Clinical Study Center, Fridley, MN, USA; ⁸Probity Medical Research and Dermatologists of the Central States, Bexley, OH, USA; ⁹Arcutis, Inc., Westlake Village, CA, USA; ¹⁰ML Trotman Consulting, LLC, Newbury Park, CA, USA.
Primary Endpoint of IGA ‘Clear’ or ‘Almost Clear’ at Week 6 Was Met for Both Roflumilast Cream Doses

Subjects Achieving IGA of ‘Clear’ or ‘Almost Clear’ at Week 6

- **Roflumilast 0.3% (n=109)**
- **Roflumilast 0.15% (n=113)**
- **Vehicle (n=109)**

*Data are presented for intent-to-treat population. CI: confidence interval; IGA: Investigator Global Assessment.*
Primary Endpoint of IGA ‘Clear’ or ‘Almost Clear’ at Week 6 Was Met for Both Roflumilast Cream Doses

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<tbody>
<tr>
<td>P&lt;0.001</td>
<td>P=0.004</td>
<td></td>
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Data are presented for intent-to-treat population. CI: confidence interval; IGA: Investigator Global Assessment.
Roflumilast Cream Improved Severity of Plaque Psoriasis

IGA: Investigator Global Assessment.

Baseline
- Roflumilast 0.3%
  - IGA = 3
- Roflumilast 0.15%
  - IGA = 3
- Vehicle
  - IGA = 3

Week 8
- Roflumilast 0.3%
  - IGA = 1
- Roflumilast 0.15%
  - IGA = 1
- Vehicle
  - IGA = 3
Most Subjects With Intertriginous Plaques Treated With Roflumilast Cream Achieved I-IGA Success by Week 6 With Continued Improvement Through Week 12

Data are presented for intent-to-treat population. CI: confidence interval; I-IGA: Intertriginous Investigator Global Assessment.