**Coacillium 22.25% cutaneous solution**

Phase 2/3 registration study in children and adolescents with moderate to severe alopecia areata (RAAINBOW)

An international, double-blind, placebo-controlled, randomised, multi-centre study

U Blume-Peytavi, BM Piraccini, P Reygagne, B Mukherjee, A Guichard, J Liu, W Pralong, S Harti

**Late breaking news presentation**
EADV 2023
Berlin, Oct 13, 2023
Disclosures

The study was sponsored by Legacy Healthcare

Ulrike Blume-Peytavi
Abbvie, Amryt, Bayer, Boots Healthcare, Cantabria Labs, Cassiopeia, CeraVe, Concert Pharmaceuticals / Sun Pharma
Dermocosmétique Vichy, Galderma Laboratorium GmbH, Lilly, Laboratoires Bailleul, Legacy Healthcare, LEO-Pharma, Mayne Pharma, Novartis, Pfizer, Sanofi Regeneron

Bianca Maria Piraccini
Almirall, Difa Cooper, Dercos-L'Oreal, Lilly, ISDIN, Legacy Healthcare, Pierre Fabre-Ducray, Pfizer

Pascal Reygagne
BMS, Concert pharmaceutical, L'Oreal research, Lilly, Novartis, Pfizer, Vichy Laboratoires

Bhawasti Mukherjee
Employed by CliniExperts Research Services Pvt. Ltd

Alexandre Guichard, Jiawei Li, William Pralong, Saad Harti
Employees and consultants for Legacy Healthcare
Remaining key unmet needs in Alopecia Areata

• An approved drug with which benefit/risk profile allows treatment of children

• An approved drug which benefit/risk profile allows early intervention
  
  • when disease is still moderate, to prevent progression to a severe stage
  
  • after first manifestation in infancy, to possibly prevent disease chronicity

• An approved drug which discontinuation does not lead to rapid disease relapse

• An approved drug which safety provides confidence for long-term compliance

• A topical drug which ease of use supports compliance
Coacillium in moderate to severe alopecia areata in children and adolescents

Baseline demographics

107 enrolled and randomized (ITT)

- 8 Evolved to SALT<25 or SALT>95 between screening and start of treatment *
- 26 were rated SALT<25 at baseline by an independent expert *
- 11 were rated SALT>95 at baseline by an independent expert *

62 FAS population

- 42 Coacillium 22,25%
- 20 Placebo

* All exclusions from FAS population were decided before unblinding

<table>
<thead>
<tr>
<th>Item</th>
<th>Total</th>
<th>Coacillium</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (ITT)</td>
<td>107</td>
<td>71 (66%)</td>
<td>36 (34%)</td>
</tr>
<tr>
<td>N (FAS)</td>
<td>62</td>
<td>42 (68%)</td>
<td>20 (32%)</td>
</tr>
<tr>
<td>Evolved to SALT&lt;25 or SALT&gt;95</td>
<td>41 (66%)</td>
<td>30 (71%)</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>Severe</td>
<td>37 (60%)</td>
<td>24 (57%)</td>
<td>13 (65%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>25 (40%)</td>
<td>18 (43%)</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Average SALT at V1</td>
<td>58</td>
<td>56.1</td>
<td>61.8</td>
</tr>
<tr>
<td>Average age</td>
<td>11</td>
<td>11.1</td>
<td>10.1</td>
</tr>
<tr>
<td>Time since onset of AA</td>
<td>3 years</td>
<td>3.3 years</td>
<td>2.5 years</td>
</tr>
<tr>
<td>Female</td>
<td>34 (55%)</td>
<td>22 (52%)</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>Patients in their 1st flare of AA</td>
<td>32 (52%)</td>
<td>21 (50%)</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>Patients with several flares</td>
<td>30 (48%)</td>
<td>21 (50%)</td>
<td>9 (45%)</td>
</tr>
</tbody>
</table>
Coacillium in moderate to severe alopecia areata in children and adolescents

Trial design

EMA requested a treatment-free follow-up of 6 months to assess disease relapse after treatment discontinuation

Primary and key secondary endpoints were analysed at 24 weeks.

No concomitant treatment for AA was allowed

The SALT score is a weighted sum of the percentage of hair loss in the 4 quadrants of the scalp, ranging from 0 (no hair loss) to 100 (complete hair loss)

SALT scoring example (adapted from Olsen 2004)

Coacillium in moderate to severe alopecia areata in children and adolescents

**Efficacy endpoints**

<table>
<thead>
<tr>
<th>Per protocol</th>
<th>Post-hoc analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1ry</strong></td>
<td>Percentage of patients achieving SALT ≤ 20</td>
</tr>
<tr>
<td>Relative change in SALT after 24 weeks of treatment</td>
<td>Percentage of patients achieving SALT ≤ 10</td>
</tr>
<tr>
<td><strong>2ry</strong></td>
<td>Proportion of subjects achieving at least a 40% relative reduction in SALT after 24 weeks treatment</td>
</tr>
<tr>
<td>Absolute change in SALT after 24 weeks of treatment</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Effect on hair follicles in non-alopecic areas by quantifying the number of new alopecic areas</td>
</tr>
<tr>
<td>Duration of treatment effect from Visit 3 (end of treatment) after 12 weeks (Visit 4) and 24 weeks (Visit 5) of treatment-free period</td>
<td>Change in CDLQI and EQ-VAS</td>
</tr>
<tr>
<td>Other*</td>
<td></td>
</tr>
</tbody>
</table>

* selection
Coacillium in moderate to severe alopecia areata in children and adolescents
Primary and key secondary endpoints were met

<table>
<thead>
<tr>
<th>Relative change in SALT after 24 weeks of treatment</th>
<th>Subjects achieving at least 40% relative reduction in SALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment effect = 31%</td>
<td>26% achieved relative reduction in SALT &gt; 40%</td>
</tr>
</tbody>
</table>

- FAS population - Relative change in SALT score 24 weeks treatment
  - Coacillium: 22.87%
  - Placebo: -8.00%
  - p < 0.0001

- FAS population
  - Proportion of patient achieving 40% relative reduction in SALT 24 weeks treatment
  - Coacillium: 26.2%
  - Placebo: 5.0%
  - p = 0.0484

Change was also superior in ITT population (p<0.0001)
Coacillium in moderate to severe alopecia areata in children and adolescents
Efficacy was positively correlated with improved quality of life

Improvement in QoL endpoints is consistent with treatment effect, in both CDLQI and EQ-5D Y endpoints
Patients express improvement in QoL as early as after 12 weeks treatment
Expressed improvement maintains after 24 weeks of treatment discontinuation

Note: CDLQI and EQ-5D Y are not specific to AA
Coacillium in moderate to severe alopecia areata in children and adolescents
Durable and continued response after treatment discontinuation

After 24 weeks, treatment is discontinued
After discontinuation, SALT score is measured after 12 weeks (week 36) and 24 weeks (week 48)

After Coacillium discontinuation, SALT continues to improve, from 44 to 29

82% of Coacillium group experienced hair growth during the treatment-free follow-up versus 37% in placebo group

Percentage of patient experiencing hair growth after treatment discontinuation

82%
37%
Coacillium in moderate to severe alopecia areata in children and adolescents

Nearly half of patients reached SALT ≤ 20, and a third reached SALT ≤ 10

<table>
<thead>
<tr>
<th>FAS population (n)</th>
<th>Baseline</th>
<th>12 weeks</th>
<th>24 weeks</th>
<th>36 weeks</th>
<th>48 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coacillium</td>
<td>42</td>
<td>38</td>
<td>33</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>Placebo</td>
<td>20</td>
<td>19</td>
<td>19</td>
<td>13</td>
<td>11</td>
</tr>
</tbody>
</table>

* p=0.0453  ** p=0.0031

* p=0.0065
Coacillium in moderate to severe alopecia areata in children and adolescents
Average SALT change for treatment responders to Coacillium was 41%

<table>
<thead>
<tr>
<th>Visit</th>
<th>Timeline</th>
<th>SALT</th>
<th>Top</th>
<th>Posterior</th>
<th>Left side</th>
<th>Right side</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1</td>
<td>Baseline</td>
<td>60</td>
<td><img src="image1.png" alt="image" /></td>
<td><img src="image2.png" alt="image" /></td>
<td><img src="image3.png" alt="image" /></td>
<td><img src="image4.png" alt="image" /></td>
</tr>
<tr>
<td>V3</td>
<td>After 24 weeks treatment</td>
<td>33</td>
<td><img src="image5.png" alt="image" /></td>
<td><img src="image6.png" alt="image" /></td>
<td><img src="image7.png" alt="image" /></td>
<td><img src="image8.png" alt="image" /></td>
</tr>
<tr>
<td>V5</td>
<td>24 weeks after discontinuation of treatment</td>
<td>8</td>
<td><img src="image9.png" alt="image" /></td>
<td><img src="image10.png" alt="image" /></td>
<td><img src="image11.png" alt="image" /></td>
<td><img src="image12.png" alt="image" /></td>
</tr>
</tbody>
</table>

Patient with 45% change during treatment period, representative of the mean
Children and adolescents with AA are more likely to have atopic dermatitis, eczema (17.4% vs. 2.2% controls) (Conic, 2020).

### Adverse Events (AEs) in RAAINBOW trial

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Coacillium (N=71)</th>
<th>Placebo (N=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n % E</td>
<td>n % E</td>
</tr>
<tr>
<td>Any AEs</td>
<td>28 (39.4%) 62</td>
<td>17 (47.2%) 42</td>
</tr>
<tr>
<td>Any SAEs</td>
<td>0</td>
<td>1 (2.8%) 2</td>
</tr>
<tr>
<td>Any TEAEs</td>
<td>28 (39.4%) 58</td>
<td>17 (47.2%) 38</td>
</tr>
<tr>
<td>Drug-related TEAEs</td>
<td>4 (5.6%) 5</td>
<td>4 (11.1%) 4</td>
</tr>
<tr>
<td>Severe TEAEs</td>
<td>1 (1.4%) 1</td>
<td>1 (2.8%) 2</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>0</td>
<td>1 (2.8%) 2</td>
</tr>
<tr>
<td>TEAEs Leading to Drug Withdrawn</td>
<td>1 (1.4%) 1</td>
<td>0</td>
</tr>
<tr>
<td>TEAEs Leading to Drug Interruption</td>
<td>1 (1.4%) 1</td>
<td>0</td>
</tr>
<tr>
<td>TEAEs Leading to Death</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

[1] Percentages are computed using N provided in the Column header.

[2] AE: Adverse Event, TEAE: Treatment Emergent Adverse Event, n: Number of subjects; E: Number of Events

**No drug-related Serious AEs**

One severe TEAE (acute eczema*)

Others are local, mild-moderate, transient

---

* Treatment was interrupted. Acute eczema stopped.
Coacillium in moderate to severe alopecia areata in children and adolescents
Composition and route of administration explain safety

Coacillium is a topically-applied, liquid, cutaneous solution

It contains 4 plant extracts classified as GRAS (Generally Regarded As Safe):
- Allium cepa
- Citrus limon
- Theobroma cacao
- Paullinia Cupana

Coacillium is regulated by EMA/FDA prescription Botanical drug status*

Coacillium in moderate to severe alopecia areata in children and adolescents
Pleitropic mode of action explains efficacy

**Effect on Immune Privilege (IP) collapse**

Adhesion molecules expressed by activated endothelial cells (EC) are essential for extravasation of immuno-inflammatory cells, a process believed to cause hair follicular IP collapse. Activated ECs are obligate interaction partners for T cells tissue-residency.

Coacillium reduces expression of pro-inflammatory adhesion molecules ICAM-1, E-selectin & the T-cell chemotaxin il-8 (by HUVEC) \(^1\) suggesting attenuation of EC activation.

**Effect on apoptotic pathway**

Significant cytotoxic T cell infiltrate and signaling molecules cause excessive apoptosis. Impaired clearance of apoptotic cells is believed to be directly linked to autoimmune diseases. The dysregulated apoptotic process leads hair follicles (HFs) to forcibly enter into catagen phase, a critical indication of IP collapse in AA development.

Analysis on scalp biopsy of subjects with androgenetic alopecia reveals that Coacillium restores Bcl-2 expression in HF cells \(^2\) towards the level identified in healthy subjects \(^3\), preventing premature onset of catagen. The observed improved expression of Ki-67 in HF cells \(^2\) represents a strong signal of enhanced cell survival capacity, indicating higher number of active cycling cells. The detected increased density of CD1A+/Langerhans \(^2\) cells in epidermis is essential for immune tolerance in scalp skin.

---

Coacillium in moderate to severe alopecia areata in children and adolescents

Conclusion

- In this phase 2-3 trial involving children and adolescents with moderate to severe alopecia areata, Coacillium cutaneous solution 22.25% twice-daily was superior to placebo after 24 weeks of treatment

- Coacillium was well tolerated

- Most Coacillium responders experienced durable response after treatment discontinuation

- Coacillium is the first drugs to show sustained remission off-treatment in alopecia areata, safely

- Coacillium might be a suitable treatment option for children and adolescents with moderate to severe AA

- Larger trials will allow better understand response to treatment
Coacillium in moderate to severe alopecia areata in children and adolescents

Acknowledgments

Thank your to all children and families!

Study Centers
Bulgaria
Petyo Brezoev
Maya Milanov
Mariyana Venelinova-Rusinova
Germany
Ulrike Blume-Peytavi
Uwe Schwichtenberg
France
Pascal Reygagne
India
Ishad Aggarwal
AS Savitha
Dipak Patel
Ashish Deshmukh
Lokesh Siddananjappa

Legacy Healthcare
Alexandre Guichard
Nadine Vincent
Cécile Bernier
Michel Chrétienne
Chris Cambourg
Jiawei Liu
William Pralong
Saad Harti