Recent Advances in Moderate to Severe AD:

**JAK Inhibitors**

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### Pipeline: Selected Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
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<tbody>
<tr>
<td><strong>TOPICAL</strong></td>
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<tr>
<td>Delgocitinib</td>
<td>JAK1, JAK2, JAK3, TYK2</td>
</tr>
<tr>
<td>E6006</td>
<td>PDE4</td>
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<tr>
<td>OPA-15406</td>
<td>PDE4</td>
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<tr>
<td>Ruxolitinib</td>
<td>JAK1 and JAK2</td>
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<tr>
<td>Tapinarof</td>
<td>AHR receptor ligand</td>
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<tr>
<td><strong>ORAL</strong></td>
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<tr>
<td>Abrocitinib</td>
<td>JAK1</td>
</tr>
<tr>
<td>ASN002</td>
<td>JAK</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>JAK1 and JAK2</td>
</tr>
<tr>
<td>Upadacitinib</td>
<td>JAK1</td>
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<tr>
<td><strong>SYSTEMIC INJECTION</strong></td>
<td></td>
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<tr>
<td>Lebrikizumab</td>
<td>IL-13</td>
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<tr>
<td>Nemolizumab</td>
<td>IL-31</td>
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<tr>
<td>Tralokinumab</td>
<td>IL-13</td>
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</tbody>
</table>

National Eczema Association.  

JAK Inhibitors: Mechanism of Action

Janus Associated Kinase

- The JAK-STAT pathway is a conserved master regulator of immunity and myeloproliferation.

- JAK inhibitors are used to treat several hematologic and inflammatory diseases.

- Small molecules (including JAK inhibitors) show improvement in AD disease scores, patient-reported outcomes, and QoL.

**JAK Inhibitors: Systemic**

- **Abrocitinib**
  - Received breakthrough therapy designation in February 2018
  - Positive topline results from phase 3 trial in patients ≥ 12 with severe disease
    - By wk 12 the proportion of patients who hit each co-primary efficacy endpoint and each key secondary endpoint with either dose, 100 mg or 200 mg, were statistically significantly higher than placebo
  - In a phase 2 trial more subjects achieved an EASI score of ≥ 50 on 4 mg dose QD than placebo
  - Multiple phase 3 trials for adults are evaluating safety and efficacy and its use as monotherapy

- **Baricitinib**
  - In a phase 2 trial more subjects achieved an EASI-50 score on 4 mg dose QD than placebo
  - All patients were on TCS for 1 month prior to initiation
  - Side effects included lymphopenia, neutropenia, AD exacerbation, and headache with no serious AEs
  - Multiple phase 3 trials for adults are evaluating safety and efficacy and its use as monotherapy

- **Upadacitinib**
  - Received breakthrough therapy designation in January 2018
  - Phase 2b trial revealed that 30 mg dose was superior to placebo in EASI score improvement and pruritus reduction
  - Phase 3 trials underway

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**Abrocitinib**

- Phase 3 randomized trial of 391 patients aged ≥12 years with moderate-to-severe AD for ≥1 year and inadequate response to topical medication for ≥4 weeks within 6 months
- At week 12, IGA 0/1 was achieved in greater proportion of patients in the 200- and 100-mg abrocitinib groups vs placebo (38.1% and 28.4% vs 9.1%, respectively; P < .001)

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**Graphs**

- **IGA response**
  - Patients with response (%) vs Treatment Time (week)
  - Placebo vs Abrocitinib 100 mg vs Abrocitinib 200 mg
  - *P < .05; †P < .001 vs placebo. Note: 95% CI graphed.

- **EASI-75 response**
  - Patients with response (%) vs Treatment Time (week)
  - Placebo vs Abrocitinib 100 mg vs Abrocitinib 200 mg
  - *P < .05; †P < .001 vs placebo. Note: 95% CI graphed.
Abrocitinib

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 78)</th>
<th>100 mg (n = 118)</th>
<th>280 mg (n = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>0</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Serious adverse events of any cause</td>
<td>1 (1.3)</td>
<td>5 (3.2)</td>
<td>2 (1.3)</td>
</tr>
</tbody>
</table>

Most frequently reported TEAEs of any cause (≥2% in any treatment group)

- Nasal congestion: 2 (2.6), 12 (7.4), 22 (14.2)
- Nasopharyngitis: 5 (6.4), 20 (13.7), 12 (7.7)
- Headache: 2 (2.6), 9 (5.7), 12 (7.7)
- Upper respiratory tract infection: 3 (3.8), 14 (8.9), 5 (3.2)
- Dermatitis atopic: 12 (15.4), 9 (5.7), 6 (3.9)
- Acne: 0, 2 (1.3), 9 (5.8)
- Vomiting: 1 (1.3), 2 (1.3), 8 (5.2)
- Upper abdominal pain: 0, 2 (1.3), 6 (3.8)
- Blood creatine phosphokinase increased: 2 (2.6), 3 (1.9), 5 (3.2)
- Fatigue: 2 (2.6), 0, 9 (5.3)
- Thrombocytopenia: 0, 0, 5 (3.2)


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Upadacitinib

- Phase 2 trial in 167 adults with moderate-to-severe AD inadequately controlled by topical treatment
- Significant improvement in EASI from baseline to week 16 with upadacitinib

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Baricitinib

- Phase 2 trial of 124 patients with moderate-to-severe AD who applied topical steroids for 4 weeks before randomization to baricitinib 2 mg or 4 mg or to placebo
- Significantly more patients who received baricitinib 4 mg achieved EASI-50 than those who received placebo (61% vs 37%; P= .027) at 16 weeks.
- TEAEs were reported in 71% of baricitinib 4 mg and 49% of placebo recipients

JAK Inhibitors: Topical

- Delgocitinib
  - Dose ranging (0.25-3% ointment) BID vs vehicle vs tacrolimus 0.1% x 4 weeks
  - All doses > vehicle in EASI (73% vs 12% in 3% group)
  - Tacrolimus = 62% reduction
  - No serious AEs

- Ruxolitinib
  - Phase 2 randomized, dose-ranging, vehicle- and active-controlled study to evaluate safety and efficacy in adult patients
    - 1.5% BID group > vehicle in EASI (71.6% improvement at 4 weeks) and noninferiority to triamcinolone cream 0.1%
    - Phase 1 study in children aged 2-17 years and two phase 3 studies (TruE-AD1 and TruE-AD2) in patients ≥12 recently completed in late 2020.

Efficacy and Safety of Ruxolitinib Cream for the Treatment of Atopic Dermatitis: Results From Two Phase 3, Randomized, Double-Blind Studies

Kim Papp, MD, PhD, 1 Jacek C. Szepietowski, MD, PhD, 2 Leon Kircik, MD, 3 Darryl Toth, MD, 4 Michael E. Kuligowski, MD, PhD, MBA, 5 May Venturanza, MD, 5 Kang Sun, PhD, 5 Eric Simpson, MD 6

1 K. Papp Clinical Research and Probit Medical Research, Waterloo, ON, Canada; 2 Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland; 3 Icahn School of Medicine at Mount Sinai, New York, NY, USA; 4 XLR8 Medical Research and Probit Medical Research, Windsor, ON, Canada; 5 Incyte Corporation, Wilmington, DE, USA; 6 Oregon Health and Science University, Portland, OR, USA

Ruxolitinib Cream

Phase 3 study:
- Vehicle-controlled 8 week BID application of:
  - 0.75% Cream
  - 1.5% Cream
  - Vehicle
- Then a 44 week additional extension study for long-term safety
  - Those already on ruxolitinib stay on, vehicle is randomized 1:1 to one of the active dosages
  - Pts treat active lesions and stop 3 days after clearance

Ruxolitinib Cream

Phase 3 study:

- **Primary endpoint:** Investigator’s Global Assessment (IGA) Treatment Success (IGA-TS) score of 0/1 with at least a 2 grade improvement at week 8
- **Secondary endpoint:** EASI-75 and Itch improvement of 4 points or more on the NRS


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Ruxolitinib Cream

Safety

- Ruxolitinib cream was well tolerated and not associated with clinically significant application site reactions
- All treatment related adverse events were mild or moderate in severity
- No treatment-emergent adverse events were suggestive of a relationship to systemic exposure

Ruxolitinib Cream

Table: Proportion of Patients with IGA-TS

<table>
<thead>
<tr>
<th></th>
<th>TRuE-AD1</th>
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<th>TRuE-AD2</th>
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<tbody>
<tr>
<td></td>
<td>Vehicle</td>
<td>0.75% RUX</td>
<td>1.5% RUX</td>
<td>Vehicle</td>
</tr>
<tr>
<td></td>
<td>(n=126)</td>
<td>(n=252)</td>
<td>(n=253)</td>
<td>(n=118)</td>
</tr>
<tr>
<td>Patients with TEAE, n (%)</td>
<td>44 (34.9)</td>
<td>74 (29.4)</td>
<td>73 (28.9)</td>
<td>40 (32.3)</td>
</tr>
<tr>
<td>Treatment-related TEAE, n (%)</td>
<td>16 (12.7)</td>
<td>15 (6.0)</td>
<td>14 (5.5)</td>
<td>12 (9.7)</td>
</tr>
<tr>
<td>Most common treatment-related TEAEs, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Application site burning</td>
<td>2 (1.6)</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>2 (1.6)</td>
<td>2 (0.8)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (1.6)</td>
<td>2 (0.8)</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>Discontinuation due to a TEAE, n (%)</td>
<td>5 (4.0)</td>
<td>3 (1.2)</td>
<td>3 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Serious TEAE, n (%)*</td>
<td>2 (1.6)</td>
<td>1 (0.4)</td>
<td>2 (0.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

Ruxolitinib Cream
At least 4 point improvement in NRS Itch Score