Apremilast, an Oral Phosphodiesterase 4 Inhibitor, in Patients With Moderate to Severe Plaque Psoriasis: Pooled Efficacy Results from the Subgroup of Canadian Patients in Two Phase III Randomized Controlled Trials (ESTEEM 1 and 2)

Kim A. Papp, MD PhD
Probity Medical Research, Waterloo, ON, Canada
Canadian PIs in ESTEEM 1 and 2

- Adam, David
- Albrecht, Lorne
- Barber, Kirk
- Bourcier, Marc
- Carey, Wayne
- Gratton, David
- Guenther, Lyn
- Kunynetz, Rodion
- Langley, Richard
- Maari, Catherine
- Papp, Kim
- Raman, Mani
- Robern, Michael
- Rosoph, Leslie
- Silver, Shane
- Tomi, Zohair
- Toth, Darryl
- Gauthier, Jean Sebastien
- Gooderham, Melinda
- Gulliver, Wayne
- Poulin, Yves
- Tan, Jerry
- Wasel, Norman
- Woolner, Derek
Disclosures / Conflicts of Interest

- Investigator
- Consultant
- Speaker
- Advisory Board Member
ESTEEM Study Population

- Adults ≥18 years of age with chronic plaque psoriasis for ≥12 months
- Moderate to severe plaque psoriasis at screening and baseline
  - Psoriasis Area and Severity Index (PASI) score ≥12
  - Body surface area ≥10%
  - Static Physician Global Assessment (sPGA) score ≥3 (moderate to severe)
  - Candidates for phototherapy or systemic therapy
- Patients with a history of prior phototherapy or systemic treatment (small molecule or biologic) or failure were permitted
ESTEEM 1 and 2: Study Design

Week 0 Week 16 Week 32 Week 52

Apremilast 30 mg BID*

Placebo

≥ PASI-75 (ESTEEM 1)
≥ PASI-50 (ESTEEM 2)

< PASI-75
< PASI-50

At time of loss of effect§

Randomize (1:2)

Screen

Long-term extension for up to 5 years

Period A

Week 0 Week

Apremilast 30 mg BID*

Apremilast 30 mg BID ± topicals, UVB‡

Apremilast 30 mg BID ± topicals, UVB‡

* Doses of apremilast were titrated during the first week of administration and at Week 16 when placebo patients were switched to apremilast. §Patients re-started apremilast at the time of loss of effect vs. baseline (loss of PASI-75, ESTEEM 1; loss of 50% of the PASI improvement obtained at Week 32, ESTEEM 2) but no later than Week 52. ‡Patients initially on placebo or randomized to apremilast 30 mg BID who did not attain PASI-75/PASI-50 were able to add topicals and/or ultraviolet B at Week 32 at the discretion of the investigator.

Korman N, et al. AAD 2015 [e-poster 1099].
**Contribution of Patients by Region**

<table>
<thead>
<tr>
<th>Region</th>
<th>ESTEEM 1</th>
<th>ESTEEM 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>35%</td>
<td>50%</td>
</tr>
<tr>
<td>Canada</td>
<td>38%</td>
<td>22%</td>
</tr>
<tr>
<td>Europe</td>
<td>14%</td>
<td>28%</td>
</tr>
<tr>
<td>Rest of World (Australia)</td>
<td>14%</td>
<td></td>
</tr>
</tbody>
</table>

24 Canadian centres, 409 patients randomized out of 1257 – 33% overall

Data on file, Celgene.
### Baseline Patient Demographics and Disease Characteristics, Full Analysis Set (N=844)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=282)</th>
<th>Apremilast 30 mg BID (n=562)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean, years</strong></td>
<td>46.5</td>
<td>45.8</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>194 (68.8)</td>
<td>379 (67.4)</td>
</tr>
<tr>
<td><strong>Duration of plaque psoriasis, mean, years</strong></td>
<td>18.7</td>
<td>19.8</td>
</tr>
<tr>
<td><strong>PASI score (0-72), mean</strong></td>
<td>19.4</td>
<td>18.7</td>
</tr>
<tr>
<td><strong>PASI &gt;20, n (%)</strong></td>
<td>87 (30.9)</td>
<td>158 (28.1)</td>
</tr>
<tr>
<td><strong>Body surface area, mean, %</strong></td>
<td>25.3</td>
<td>24.4</td>
</tr>
<tr>
<td><strong>Body surface area &gt;20%, n (%)</strong></td>
<td>149 (52.8)</td>
<td>266 (47.3)</td>
</tr>
<tr>
<td><strong>sPGA = 4 (severe), n (%)</strong></td>
<td>89 (31.6)</td>
<td>161 (28.6)</td>
</tr>
<tr>
<td><strong>ScPGA score ≥3, n (%)</strong></td>
<td>189 (67.0)</td>
<td>374 (66.5)</td>
</tr>
<tr>
<td><strong>DLQI score (0-30), mean</strong></td>
<td>12.2</td>
<td>12.7</td>
</tr>
<tr>
<td><strong>ScPGA score ≥3, n (%)</strong></td>
<td>189 (67.0)</td>
<td>374 (66.5)</td>
</tr>
<tr>
<td><strong>NAPSI score for target nail</strong></td>
<td>12 (4.3)</td>
<td>12 (4.3)</td>
</tr>
<tr>
<td><strong>Prior systemic therapy (conventional +/- biologic), n (%)</strong></td>
<td>150 (53.2)</td>
<td>301 (53.6)</td>
</tr>
<tr>
<td><strong>Prior conventional systemic therapy, n (%)</strong></td>
<td>102 (36.2)</td>
<td>212 (37.7)</td>
</tr>
<tr>
<td><strong>Prior biologic therapy, n (%)</strong></td>
<td>80 (28.4)</td>
<td>162 (28.8)</td>
</tr>
</tbody>
</table>

The n reflects the number of patients who were randomized; actual number of patients available for each endpoint may vary. *n=195 (placebo) and n=366 (apremilast 30 mg BID). VAS=visual analog scale; DLQI=Dermatology Life Quality Index; ScPGA=Scalp Physician’s Global Assessment; NAPSI=Nail Psoriasis Severity Index.

Papp K, et al. AAD 2014 [e-poster 8359].
Baseline Patient Demographics and Disease Characteristics: Full Analysis Set (N=411)

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=137</th>
<th>Apremilast 30 mg BID n=274</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, years</td>
<td>45.7</td>
<td>45.3</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>100 (73.0)</td>
<td>176 (64.2)</td>
</tr>
<tr>
<td>Body mass index, mean, kg/m²</td>
<td>30.7</td>
<td>30.9</td>
</tr>
<tr>
<td>Duration of plaque psoriasis, mean, years</td>
<td>18.7</td>
<td>17.9</td>
</tr>
<tr>
<td>PASI score (0–72), mean</td>
<td>20.0</td>
<td>18.9</td>
</tr>
<tr>
<td>PASI &gt;20, n (%)</td>
<td>49 (35.8)</td>
<td>81 (29.6)</td>
</tr>
<tr>
<td>Body surface area, mean, %</td>
<td>27.6</td>
<td>25.5</td>
</tr>
<tr>
<td>Body surface area &gt;20%, n (%)</td>
<td>80 (58.4)</td>
<td>143 (52.2)</td>
</tr>
<tr>
<td>sPGA = 4 (severe), n (%)</td>
<td>49 (35.8)</td>
<td>75 (27.4)</td>
</tr>
<tr>
<td>Pruritus VAS score (0–100 mm), mean</td>
<td>65.3</td>
<td>67.7</td>
</tr>
<tr>
<td>DLQI score (0–30), mean</td>
<td>12.8</td>
<td>12.6</td>
</tr>
<tr>
<td>ScPGA score ≥3, n (%)</td>
<td>93 (67.9)</td>
<td>176 (64.2)</td>
</tr>
<tr>
<td>NAPSI score for target nail, mean*</td>
<td>4.4</td>
<td>4.2</td>
</tr>
<tr>
<td>Prior systemic therapy (conventional +/- biologic), n (%)</td>
<td>73 (53.3)</td>
<td>157 (57.3)</td>
</tr>
<tr>
<td>Prior conventional systemic therapy, n (%)</td>
<td>53 (38.7)</td>
<td>106 (38.7)</td>
</tr>
<tr>
<td>Prior biologic therapy, n (%)</td>
<td>44 (32.1)</td>
<td>92 (33.6)</td>
</tr>
</tbody>
</table>

The n reflects the number of patients who were randomized; actual number of patients available for each endpoint may vary. *n=91 (placebo) and n=175 (apremilast 30 mg BID). VAS=visual analog scale; DLQI=Dermatology Life Quality Index; ScPGA=Scalp Physician Global Assessment; NAPSI=Nail Psoriasis Severity Index.

Paul C, et al. AAD 2014 [e-poster 8412].
**Canadian Baseline Patient Demographics and Disease Characteristics: Full Analysis Set (N=409)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=136</th>
<th>Apremilast 30 mg BID n=273</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, years</td>
<td>48.6</td>
<td>45.5</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>99 (72.8)</td>
<td>175 (64.1)</td>
</tr>
<tr>
<td>Body mass index, mean, kg/m²</td>
<td>32.24</td>
<td>31.53</td>
</tr>
<tr>
<td>Duration of plaque psoriasis, mean years</td>
<td>20.46</td>
<td>19.45</td>
</tr>
<tr>
<td>PASI score (0-72), mean</td>
<td>18.22</td>
<td>17.95</td>
</tr>
<tr>
<td>PASI &gt;20, n (%)</td>
<td>39 (28.7)</td>
<td>62 (22.7)</td>
</tr>
<tr>
<td>Body surface area, mean, %</td>
<td>22.31</td>
<td>21.56</td>
</tr>
<tr>
<td>Body surface area &gt;20%, n (%)</td>
<td>60 (44.1)</td>
<td>100 (36.6)</td>
</tr>
<tr>
<td>sPGA = 4 (severe), n (%)</td>
<td>48 (35.3)</td>
<td>84 (30.8)</td>
</tr>
<tr>
<td>Pruritus VAS score (0-100 mm), mean</td>
<td>65.4</td>
<td>67.8</td>
</tr>
<tr>
<td>DLQI score (0-30), mean</td>
<td>11.7</td>
<td>12.6</td>
</tr>
<tr>
<td>ScPGA score ≥3, n (%)</td>
<td>50 (36.8)</td>
<td>120 (44.0)</td>
</tr>
<tr>
<td>NAPSI score for target nail, mean*</td>
<td>3.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Prior systemic therapy (conventional +/- biologic), n (%)</td>
<td>65 (47.8)</td>
<td>113 (41.4)</td>
</tr>
<tr>
<td>Prior conventional systemic therapy, n (%)</td>
<td>43 (31.6)</td>
<td>78 (28.6)</td>
</tr>
<tr>
<td>Prior biologic therapy, n (%)</td>
<td>37 (27.2)</td>
<td>58 (21.2)</td>
</tr>
</tbody>
</table>

The n reflects the number of patients who were randomized; actual number of patients available for each end point may vary.

Data on file, Celgene.
The full analysis set included all patients who were randomized according to protocol. The safety population included all patients who were randomized and received ≥1 dose. *One death occurred in a patient randomized to apremilast 30 mg BID after receiving the last dose of study medication in the placebo-controlled phase. The patient was considered to have completed the placebo-controlled phase.

Reich K, et al. AAD 2013 [LB oral presentation]
The full analysis set included all patients who were randomized according to protocol. 139 patients were randomized to placebo and 275 to apremilast 30 mg BID; however, 1 patient randomized to placebo and 1 patient randomized to apremilast 30 mg BID were randomized in error and did not have investigational product dispensed; these patients were excluded from the full analysis set. The safety population included all patients who were randomized and received ≥1 dose.

Paul C, et al. AAD 2014 [e-poster 8412].
Canadian Sites: Subject Disposition Weeks 0–16

Randomized (1:2) N=409

Placebo n=136

Placebo n=136

Apremilast 30 mg BID n=273

Apremilast 30 mg BID n=273

Discontinued (n=11) 8.1%
- Adverse event 1
- Lack of efficacy 3
- Noncompliance with study drug 0
- Withdrawal by subject 4
- Lost to follow-up 3
- Protocol violation 0
- Other 1

Discontinued (n=25) 9.2%
- Adverse event 8
- Lack of efficacy 0
- Noncompliance with study drug 4
- Withdrawal by subject 8
- Lost to follow-up 3
- Protocol violation 2
- Other 0

Completed 16 Weeks n=125 (91.9%)

Completed 16 weeks n=248 (90.8%)

The full analysis set (ITT population) included all subjects who were randomized according to protocol. The safety population included all subjects who were randomized and received ≥1 dose.

Data on file, Celgene.
PASI-75 and PASI-50 at Week 16

*P<0.0001 vs. placebo.
LOCF=last observation carried forward.

sPGA at Week 16

Full Analysis Set, LOCF

*P<0.0001 vs. placebo.
sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline
LOCF=last observation carried forward.

### Adjusted Difference in PASI-75 Response Rate

**(APR 30 BID vs Placebo)**

**LOCF, Full Analysis Set**

<table>
<thead>
<tr>
<th>Baseline PASI Score</th>
<th>Overall In favor of placebo</th>
<th>Act. vs Placebo</th>
<th>Adj. Diff (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 20</td>
<td>265/836 (31.7) vs 23/419 (5.5)</td>
<td>26.2 (22.4, 30.0)</td>
<td></td>
</tr>
<tr>
<td>&gt; 20</td>
<td>205/597 (34.3) vs 17/283 (6.0)</td>
<td>28.4 (23.7, 33.1)</td>
<td></td>
</tr>
<tr>
<td>Baseline sPGA Score</td>
<td>Overall In favor of apremilast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 20</td>
<td>60/239 (25.1) vs 6/136 (4.4)</td>
<td>20.7 (14.2, 27.2)</td>
<td></td>
</tr>
<tr>
<td>&gt; 20</td>
<td>202/599 (33.7) vs 19/280 (6.8)</td>
<td>27.0 (22.2, 31.8)</td>
<td></td>
</tr>
<tr>
<td>Baseline BSA (%) Category</td>
<td>Overall Act. vs Placebo</td>
<td>Adj. Diff (95% CI)</td>
<td></td>
</tr>
<tr>
<td>≤ 20</td>
<td>140/427 (32.8) vs 9/190 (4.7)</td>
<td>28.1 (22.7, 33.5)</td>
<td></td>
</tr>
<tr>
<td>&gt; 20</td>
<td>125/409 (30.8) vs 14/229 (6.1)</td>
<td>24.4 (19.0, 29.9)</td>
<td></td>
</tr>
</tbody>
</table>

**ESTEEM 1&2**

### PASI-75 Response Rate (Week 16) APR 30 BID

**LOCF, Full Analysis Set**

<table>
<thead>
<tr>
<th></th>
<th>Global</th>
<th>Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline PASI &lt;=20 (inclusion criteria &gt;12)</td>
<td>34.3</td>
<td>38.9</td>
</tr>
<tr>
<td>Baseline BSA% &lt;=20 (inclusion criteria &gt;10%)</td>
<td>32.8</td>
<td>41.6</td>
</tr>
</tbody>
</table>

**ESTEEM 1&2**
Mean Change from Baseline in DLQI at Week 16
LOCF, Full Analysis Set

ESTEEM 1
Baseline DLQI Score (mm) 12.1
LS Mean Change From Baseline in Pruritus VAS (mm)
-2.1 n=274

ESTEEM 2
Baseline DLQI Score (mm) 12.7
LS Mean Change From Baseline in Pruritus VAS (mm)
-6.6 n=556

ESTEEM 1&2
Baseline DLQI Score (mm) 65.0
LS Mean Change From Baseline in Pruritus VAS (mm)
-6.7 n=131

Baseline DLQI Score (mm) 67.8
LS Mean Change From Baseline in Pruritus VAS (mm)
-6.7 n=267

Placebo
Apremilast 30 mg BID

\(^aP<0.0001\) vs placebo
LOCF = Last observation carried forward.

Reich K, et al. AAD 2013 [LB oral presentation].
Pruritus VAS at Week 16
LOCF, Full Analysis Set

**Pruritus Visual Analog Scales (VAS) values range from 0 to 100. Higher scores correspond to worse pruritus (itch).**

**LOCF = Last observation carried forward. Subjects with a baseline value and at least one post-baseline value are included.**

Pruritus VAS at Week 16
LOCF, Full Analysis Set

**ESTEEM 1**
- Baseline VAS Score (mm): 65.2
- LS Mean Change From Baseline in Pruritus VAS (mm): -7.3
- n=282

**ESTEEM 2**
- Baseline VAS Score (mm): 66.2
- LS Mean Change From Baseline in Pruritus VAS (mm): -12.2
- n=562

**ESTEEM 1&2**
- Baseline VAS Score (mm): 65.4
- LS Mean Change From Baseline in Pruritus VAS (mm): -9.3
- n=133

- Baseline VAS Score (mm): 67.8
- LS Mean Change From Baseline in Pruritus VAS (mm): -37.2
- n=272

*P<0.0001 vs placebo

Pruritus Visual Analog Scales (VAS) values range from 0 to 100. Higher scores correspond to worse pruritus (itch).

LOCF = Last observation carried forward. Subjects with a baseline value and at least one post-baseline value are included.

Conclusion

Apremilast improved the signs and symptoms of moderate to severe plaque psoriasis in the subgroup of Canadian patients