**Efficacy and Safety of Apremilast, an Oral Phosphodiesterase Inhibitor, in Ankylosing Spondylitis**


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On behalf of the Spondylitis Trial of Apremilast for better Rheumatic Therapy (START) Study Group

**Disclosure**

P.C. Taylor – Dr. Taylor has received an unrestricted research grant from Celgene and is an invited advisory board member.

**ASAS/EULAR Recommendations for the Management of AS**

- **NSAIDs**
  - Axial disease
  - Peripheral disease
  - Sulfasalazine
  - Local corticosteroids
  - TNF-α blockers

**Apremilast**

- Apremilast is a novel, orally available small molecule that specifically targets PDE4, an intracellular enzyme that modulates expression of a network of pro- and anti-inflammatory mediators
- Pharmacokinetics of apremilast in humans:
  - AUC and C_{max} increase in dose-related manner from 10 to 100 mg/day
  - T_{max}: 1–3 hours (single and multiple dose)
  - t_{1/2}: 5–7 hours across all doses

**Apremilast Modulates the Production of Pro-inflammatory and Anti-inflammatory Mediators**

**Apremilast: Anti-inflammatory Activity In Vitro and in a Model of Psoriasis**

**Grafts A and B:**

- Histopathological features of psoriasis are observed

**11/7/2011**
Apremilast in PsA: ACR Response at Week 12
ITT Population (LOCF); N=204

versus placebo.
ACR20, ACR50, ACR70=American College of Rheumatology criteria for 20%, 50%, and 70% improvement;
ITT=intent to treat; LOCF=last observation carried forward; PsA=psoriatic arthritis.

Aims

• To explore the effect of apremilast on the signs and symptoms of ankylosing spondylitis
• To explore the safety and tolerability of apremilast in ankylosing spondylitis
• To investigate the effect of apremilast on exploratory biomarkers of bone biology in ankylosing spondylitis

Inclusion/Exclusion Criteria

• Inclusion criteria
  – Ankylosing spondylitis defined by the modified New York criteria (1984), with symptoms for ≥2 years
  – Age ≥18 years
  – Patients must have a score of >1 on questions 2 and 5 of the BASDAI score for the 2 weeks prior to randomisation
  – Evidence of bone oedema on MRI at baseline at either sacroiliac joint or spine to suggest active disease

• Exclusion criteria
  – Use of DMARDs within 8 weeks of randomisation
  – Use of steroids within 4 weeks of randomisation
  – Use of etanercept within 4 weeks, adalimumab within 10 weeks, or infliximab within 12 weeks of randomisation

Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Index Measured</th>
<th>Placebo (n=19) Mean (SD)</th>
<th>Apremilast (n=17) Mean (SD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39.21 (13.3)</td>
<td>44.88 (11.1)</td>
<td>0.17</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>18.39 (10.17)</td>
<td>20.88 (12.32)</td>
<td>0.51</td>
</tr>
<tr>
<td>BASDAI</td>
<td>4.36 (1.757)</td>
<td>4.79 (2.161)</td>
<td>0.52</td>
</tr>
<tr>
<td>BASFI</td>
<td>3.49 (2.208)</td>
<td>4.55 (2.429)</td>
<td>0.178</td>
</tr>
<tr>
<td>BASMI</td>
<td>3.16 (1.598)</td>
<td>4.48 (1.963)</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Assessment of Clinical Efficacy: Activity Criteria

• Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
  – A composite index consisting of a visual analogue scale evaluation of fatigue, axial pain, peripheral pain, stiffness, and enthesopathy

• Bath Ankylosing Spondylitis Functional Index (BASFI)
  – To define mobility and monitor functional ability

• Bath Ankylosing Spondylitis Metrology Index (BASMI)
  – To assess axial status and to define clinically significant changes in spinal movement
Assessment of Clinical Efficacy

### BASDAI: Change From Baseline

- **Apremilast**
- **Placebo**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Day</th>
<th>Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>8</td>
<td>-0.25</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>-0.00</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>-0.25</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>-0.50</td>
</tr>
<tr>
<td>8</td>
<td>85</td>
<td>-0.75</td>
</tr>
<tr>
<td>9</td>
<td>113</td>
<td>-1.00</td>
</tr>
</tbody>
</table>

### BASFI: Change From Baseline

- **Apremilast**
- **Placebo**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Day</th>
<th>Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>8</td>
<td>-0.77 (1.47)</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>-1.59 (1.48)</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>-0.28 (1.61)</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>-1.74 (1.91)</td>
</tr>
<tr>
<td>8</td>
<td>85</td>
<td>-0.21 (1.02)</td>
</tr>
<tr>
<td>9</td>
<td>113</td>
<td>-0.51 (1.02)</td>
</tr>
</tbody>
</table>

### BASMI: Change From Baseline

- **Apremilast**
- **Placebo**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Day</th>
<th>Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>8</td>
<td>-0.25</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>-0.00</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>-0.25</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>-0.50</td>
</tr>
<tr>
<td>8</td>
<td>85</td>
<td>-0.75</td>
</tr>
<tr>
<td>9</td>
<td>113</td>
<td>-1.00</td>
</tr>
</tbody>
</table>

**Results: Clinical Response**

<table>
<thead>
<tr>
<th>Mean Change After 12 Weeks From Baseline (SD)</th>
<th>Placebo (n=19)</th>
<th>Apremilast (n=17)</th>
<th>P Value (ANCOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASDAI</td>
<td>-0.77 (1.47)</td>
<td>-1.59 (1.48)</td>
<td>0.139</td>
</tr>
<tr>
<td>BASFI</td>
<td>-0.28 (1.61)</td>
<td>-1.74 (1.91)</td>
<td>0.108</td>
</tr>
<tr>
<td>BASMI</td>
<td>-0.21 (1.02)</td>
<td>-0.51 (1.02)</td>
<td>0.617</td>
</tr>
</tbody>
</table>

**Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n=19)</th>
<th>Apremilast (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>5 (26.3%)</td>
<td>8 (42.1%)</td>
</tr>
<tr>
<td>Loose stools</td>
<td>2 (10.5%)</td>
<td>5 (26.3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (15.8%)</td>
<td>3 (15.8%)</td>
</tr>
<tr>
<td>URTI</td>
<td>6 (31.6%)</td>
<td>6 (31.6%)</td>
</tr>
<tr>
<td>Diarrhoea*</td>
<td>2 (10.5%)</td>
<td>2 (10.5%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (10.5%)</td>
<td>1 (5.3%)</td>
</tr>
<tr>
<td>Poor concentration*</td>
<td>1 (5.3%)</td>
<td>1 (5.3%)</td>
</tr>
<tr>
<td>Irregular pulse (sinus tachycardia)</td>
<td>0</td>
<td>1 (5.3%)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>(V/E stopped spontaneously)</td>
<td>0</td>
</tr>
</tbody>
</table>

*The majority (68.4%) of all adverse events were mild; no serious adverse events were reported.

Serum Biomarkers: %△RANKL and OPG

<table>
<thead>
<tr>
<th>Change in RANKL With Treatment</th>
<th>OPG With Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apremilast Treatment Group</td>
<td>Placebo Treatment Group</td>
</tr>
<tr>
<td>P-value</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Excluding 1 value in 1 patient on apremilast where the baseline value was undetectable but follow-up value was 4 pmol/L.

RANKL = receptor activator of nuclear factor kappa-B ligand; OPG = osteoprotegerin.
Plasma Biomarkers: Sclerostin %Δ

% Change in Plasma Sclerostin With Treatment

Apremilast Placebo

Treatment Groups

Future Work: Analysis of MRI STIR

Resolution of Posterior and Anterior Corner Lesions

Pre-treatment Post-treatment

Anterior and Posterior Corner Lesions Showing Improvement

Pre-treatment Post-treatment

• Failure of improvement in Anderson lesion in same patient in apremilast group

MRI=magnetic resonance imaging; STIR=short T1 inversion recovery.

Conclusions

• Trend towards improvement on treatment of ankylosing spondylitis patients with apremilast
  - Allows for adequately powered study to obtain statistically significant results
  - Apremilast has an acceptable safety profile in this short-term pilot study
  - Apremilast modulates bone biomarkers
  - Results suggest that the efficacy and safety of apremilast in ankylosing spondylitis may mirror effects in other inflammatory disorders
  - Although a small study, START supports further research of apremilast in axial disease
    - Phase III study in ankylosing spondylitis is planned
    - Phase III studies in psoriatic arthritis and psoriasis are ongoing

START=Spondylitis Trial of Apremilast for better Rheumatic Therapy.

Acknowledgements

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Principal Investigator
  • Peter C Taylor

Co-Investigators
  • Sonya Abraham
  • Andrew Keat
  • Robin Withrington
  • Liz Van Rossen

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