PSYCHIATRIC ADVERSE EVENTS IN BRODALUMAB PSORIASIS STUDIES

Mark Lebwohl,¹ Kim A. Papp,² Jashin J. Wu,³ Andrew Blauvelt,⁴ Alan Menter,⁵ Shipra Rastogi,⁶ Radhakrishnan Pillai,⁷ Robert Israel⁶

¹Icahn School of Medicine at Mount Sinai, New York, NY, USA; ²Probity Medical Research, Waterloo, Ontario, Canada; ³Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA, USA; ⁴Oregon Medical Research Center, Portland, OR, USA; ⁵Baylor University Medical Center, Dallas, TX, USA; ⁶Valeant Pharmaceuticals North America LLC, Bridgewater, NJ, USA; ⁷Dow Pharmaceutical Sciences (a division of Valeant Pharmaceuticals North America LLC), Petaluma, CA, USA

This study was sponsored by Valeant Pharmaceuticals North America LLC. Medical writing support was provided by MedThink SciCom and funded by Valeant Pharmaceuticals North America LLC.
**INTRODUCTION**

- Psoriasis has profound psychosocial implications that can affect the ability of patients to socialize with family members, interact with coworkers, and make friends\(^1\).
- Psychiatric comorbidities, such as depression and anxiety, are common in patients with psoriasis\(^2,3\).
- Suicidal ideation has been reported in as many as 17.3% of patients with psoriasis compared with 8.3% of healthy controls\(^4\).
- Brodalumab is a monoclonal antibody that targets interleukin-17 (IL-17) receptor A and is under investigation for use in the treatment of psoriasis\(^5\).
- Brodalumab has demonstrated efficacy in the treatment of plaque psoriasis\(^5,6\).
- Reports of suicide in patients with psoriasis enrolled in clinical trials for brodalumab led to concerns that brodalumab may be linked to psychiatric adverse events (AEs)\(^6,7\).

**OBJECTIVE**

- To assess psychiatric AEs and improvements in depression and anxiety in patients with psoriasis treated with brodalumab in clinical trials.

---

Methods

Clinical Studies
• Efficacy and safety of brodalumab (140 or 210 mg every 2 weeks [Q2W]) were investigated in one phase 2 trial and in three phase 3, multicenter, randomized trials of patients with moderate-to-severe plaque psoriasis (AMAGINE-1/-2/-3)\(^1,2\)
• In the phase 3 studies, more than 80% of patients were being treated with brodalumab 210 mg Q2W by the end of the week 52 controlled period
• There were no specific exclusion criteria for psychiatric disorders or substance abuse

Endpoints
• The hospital anxiety and depression scale (HADS), which determines anxiety and depression on a 21-point scale each, was measured in AMAGINE-1
• The dermatology life quality index (DLQI) assesses the socio-psychological impact of the skin disease\(^3\) on patients’ lives and was measured in AMAGINE-1/-2/-3
• Data on psychiatric AEs were pooled for all trials and were summarized as follow-up time–adjusted event rates
  • The follow-up time–adjusted event rate is the total number of events reported during the follow-up observation time divided by total patient-years of observation; this includes gaps and interruptions in exposure and time beyond the exposure period

Changes in HADS Severity at Week 12

RESULTS

Figure 1. Shifts in HADS severity at week 12 in patients who scored “moderate” or “severe” at baseline in the AMAGINE-1 trial.

HADS, hospital anxiety and depression scale; Q2W, every 2 weeks.
Shifts in HADS severity at week 12 in patients who scored “moderate” or “severe” at baseline.
*Data are shown as observed; percentages do not add to 100%.
Improvements in Patient Satisfaction in Those Treated With Brodalumab

RESULTS (cont)
Figure 2. DLQI 0/1 response rate at week 12 in patients from the AMAGINE-1, -2, and -3 trials.

DLQI 0/1 response to treatment

<table>
<thead>
<tr>
<th></th>
<th>AMAGINE-1</th>
<th>AMAGINE-2</th>
<th>AMAGINE-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>5%</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>43%</td>
<td>44%</td>
<td>44%</td>
</tr>
<tr>
<td>140 mg Q2W</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>210 mg Q2W</td>
<td>56%</td>
<td>47%</td>
<td>43%</td>
</tr>
</tbody>
</table>

DLQI, dermatology life quality index.
DLQI response = score 0/1.
*P<0.001 vs placebo.
# Psychiatric Adverse Events

## RESULTS (cont)

**Table 1.** Incidence of Psychiatric Adverse Events Occurring in ≥0.1% of Patients Treated With Brodalumab During the Initial Placebo-Controlled Study Period

<table>
<thead>
<tr>
<th>Preferred term, n (%)</th>
<th>Placebo (N=879)</th>
<th>Ustekinumab (N=613)</th>
<th>Brodalumab(^b) (N=3066)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorders SOC</td>
<td>16 (1.8)</td>
<td>12 (2.0)</td>
<td>61 (2.0)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6 (0.7)</td>
<td>4 (0.7)</td>
<td>17 (0.6)</td>
</tr>
<tr>
<td>Depression</td>
<td>5 (0.6)</td>
<td>3 (0.5)</td>
<td>14 (0.5)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2 (0.2)</td>
<td>2 (0.3)</td>
<td>13 (0.4)</td>
</tr>
<tr>
<td>Libido decreased</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>5 (0.2)</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>1 (0.1)</td>
<td>2 (0.3)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Mood swings</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Stress</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td>3 (0.1)</td>
</tr>
</tbody>
</table>

SOC, system organ class.

\(^a\)Includes data from the placebo-controlled phase 2 study, AMAGINE-1, AMAGINE-2, and AMAGINE-3. \(^b\)All brodalumab dose groups combined.
### Results (cont)

**Table 2.** Integrated Analysis of Follow-up Time-Adjusted Patient Incidence Rates of SIB Events Through Week 52 and in Long-term Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Ustekinumab (N=613; pt-yr = 503.6)</th>
<th>Brodalumab (N=4019; pt-yr = 3545.7)</th>
<th>Brodalumab (N=4464; pt-yr = 9161.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (r) [95% CI]</td>
<td>n (r) [95% CI]</td>
<td>n (r) [95% CI]</td>
</tr>
<tr>
<td><strong>Suicidal ideation adverse event</strong></td>
<td>1 (0.20) [0.01, 1.11]</td>
<td>3 (0.08) [0.02, 0.25]</td>
<td>22 (0.24) [0.15, 0.36]</td>
</tr>
<tr>
<td><strong>Suicidal behavior adverse event</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed suicide⁹⁴</td>
<td>1 (0.20) [0.01, 1.11]</td>
<td>4 (0.11) [0.03, 0.29]</td>
<td>15 (0.16) [0.09, 0.27]</td>
</tr>
<tr>
<td>Intentional self-injury</td>
<td>0 (0.00) [0.00, 0.73]</td>
<td>2 (0.06) [0.01, 0.20]</td>
<td>4 (0.04) [0.01, 0.11]</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>0 (0.00) [0.00, 0.73]</td>
<td>1 (0.03) [&lt;0.01, 0.16]</td>
<td>1 (0.01) [0.00, 0.06]</td>
</tr>
<tr>
<td>Suicidal behavior</td>
<td>1 (0.20) [0.01, 1.11]</td>
<td>1 (0.03) [&lt;0.01, 0.16]</td>
<td>6 (0.07) [0.02, 0.14]</td>
</tr>
<tr>
<td></td>
<td>0 (0.00) [0.00, 0.73]</td>
<td>0 (0.00) [0.00, 0.10]</td>
<td>4 (0.04) [0.01, 0.11]</td>
</tr>
<tr>
<td><strong>Overall suicidal ideation and behavior</strong></td>
<td>2 (0.40) [0.05, 1.44]</td>
<td>7 (0.20) [0.08, 0.41]</td>
<td>34 (0.37) [0.26, 0.52]</td>
</tr>
</tbody>
</table>

- There were 22 suicidal ideations (follow-up time–adjusted rate, 0.24), 6 suicide attempts (0.07), 3 completed suicides (0.03), and 1 additional suicide adjudicated as indeterminate.

SIB, suicidal ideation and behavior.

⁹⁴Cumulative events through the 52-week, controlled treatment period. ⁹⁵Includes events in the 52-week treatment period and the uncontrolled open-label extension. ⁹⁶Includes fatal event reported as intentional overdose that was adjudicated as indeterminate.
## RESULTS (cont)

**Table 3. Summary of Completed Suicides (Known and Unknown Cause)**

<table>
<thead>
<tr>
<th>Age, y/ Sex</th>
<th>Brodalumab dose</th>
<th>Clinical response (PASI score)</th>
<th>Clinical information</th>
</tr>
</thead>
</table>
| 59/Male     | 210 mg          | 100                          | • 329 days after first dose of brodalumab  
• History of financial stressors (lost disability due to brodalumab response and unable to find work) |
| 39/Male     | 210 mg          | 73                           | • 140 days after first dose of brodalumab  
• Informed investigator he had legal difficulties and was likely to be incarcerated  
• Family reported he killed himself, means unknown |
| 56/Male     | 210 mg          | 100                          | • 845 days after first dose of brodalumab  
• Ongoing treatment for depression and anxiety  
• Described recent stress and isolation due to relocation |

**Indeterminate case**

<table>
<thead>
<tr>
<th>Age, y/ Sex</th>
<th>Brodalumab dose</th>
<th>Clinical response (PASI score)</th>
<th>Clinical information</th>
</tr>
</thead>
</table>
| 56/Male     | 210 mg          | 100                          | • History of depression; on antidepressant and benzodiazepine  
• 97 days after first dose of brodalumab  
• Toxic levels of mixed opiates compatible with ingestion of poppy seed tea and methadone; therapeutic level of citalopram, elevated alprazolam, and alcohol  
• HADS baseline depression and anxiety score decreased from 15 to 2 and 14 to 6, respectively, 2 weeks before the event  
• Ruled indeterminate by C-CASA adjudication |

C-CASA, Columbia classification algorithm of suicide assessment; HADS, hospital anxiety and depression scale; PASI, psoriasis area and severity index.
Results (cont)

- Two SIB events (suicide attempts) were reported in 1 patient treated with brodalumab during the 12-week induction phase (0.03%; 1/3066)

- Follow-up time–adjusted rates of SIB were greater in patients with a history of depression compared with those without (1.42 and 0.21 per 100 patient-years, respectively)

- Follow-up time–adjusted rates of SIB were greater in patients with a history of suicidality compared with those without (3.21 and 0.20 per 100 patient-years, respectively)

SIB, suicidal ideation and behavior.
Summary and Conclusions

- Median HADS anxiety and depression scores were reduced from baseline in patients with moderate-to-severe plaque psoriasis receiving brodalumab.
- A higher patient satisfaction and quality of life was observed with brodalumab compared with placebo, as determined by DLQI response rate.
- Rates of SIB at week 52 in patients treated with brodalumab were similar to those treated with the active comparator ustekinumab, and SIB rates did not increase with long-term treatment.
- No pattern emerged between timing of the events and the initiation or withdrawal of brodalumab.
- Controlled data do not suggest a causal relationship between brodalumab treatment and SIB.

DLQI, dermatology life quality index; HADS, hospital anxiety and depression scale; SIB, suicidal ideation and behavior.