IMO-3100, an antagonist of Toll-like receptor (TLR) 7 and TLR9, demonstrates clinical activity in psoriasis patients with 4 weeks of treatment in a Phase 2a trial

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Introduction

Psoriasis is a chronic autoimmune disease in which nucleic acids released from damaged skin form complexes with host peptides and subsequently engage endosomal Toll-like receptors (TLRs) 7, 8, and 9, triggering signaling cascades and inducing cytokines, including TNF-α, IL-12/23, IL-17. Currently, most therapies target these downstream products.

Endosomal TLRs were selected as a target for the treatment of psoriasis and other autoimmune diseases based on the goal of blocking the inflammatory response upstream of immune cell activation and cytokine induction.

IMO-3100 is an oligonucleotide antagonist of TLR7 and 9 administered once weekly by subcutaneous injection. In Phase 1, dosages of 0.16 and 0.32 mg/kg showed target engagement, and were selected for a proof-of-concept study of TLR antagonism.

Protocol 3100-202 was a randomized, placebo-controlled, double-blind, 4-week trial of IMO-3100 monotherapy. A total of 44 adults with moderate to severe plaque psoriasis were enrolled at 11 sites in the US (Apr to Sep 2012).
Endosomal TLRs in the Pathogenesis of Psoriasis

Injury or infection

Stressed keratinocytes

IL-12

IL-23

Th1 cell

Th17 cell

TNF-α

Interferon-γ

Inflammation

More immune cells recruited/activated

Keratinocyte division plaque formation

Keratinocyte production

Endosomal TLRs on dendritic cells and keratinocytes

Cytokines

Cytokine production

More immune cells recruited/activated
# Study Events

<table>
<thead>
<tr>
<th>Day</th>
<th>Scr</th>
<th>1</th>
<th>8</th>
<th>15</th>
<th>22</th>
<th>29</th>
<th>36</th>
<th>57</th>
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<tr>
<td>Dosing</td>
<td>✔️</td>
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<td>✔️</td>
<td>✔️</td>
<td></td>
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<td></td>
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<tr>
<td>PASI</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
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<td>Biopsy</td>
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## Patient Demographics and Disposition

<table>
<thead>
<tr>
<th></th>
<th>0.16 mg/kg</th>
<th>0.32 mg/kg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled(^1)</td>
<td>15</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Age, years</td>
<td>36 (20-68)</td>
<td>40 (19-59)</td>
<td>40 (24-69)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77 (55-117)</td>
<td>93 (57-121)</td>
<td>95 (67-122)</td>
</tr>
<tr>
<td>Day 1 PASI</td>
<td>15 (10-36)</td>
<td>16 (10-25)</td>
<td>13 (10-28)</td>
</tr>
<tr>
<td>White (%)</td>
<td>100%</td>
<td>86%</td>
<td>87%</td>
</tr>
<tr>
<td>Clin Eval(^2)</td>
<td>12</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>

\(^1\) Randomized & received ≥1 dose.

\(^2\) Excludes 1 pt withdrawal of consent; 2 pts lost to follow-up (Storm Sandy); 1 non-qualifying disease.
Safety and Tolerability

• IMO-3100 treatment was well-tolerated. There were no treatment-related discontinuations and no changes in laboratory parameters.
• The most common treatment-related adverse events were mild injection sites reactions of erythema, sometimes with induration.
• Other treatment-related events were reported in 3 pts in each IMO-3100 dose cohort and in 2 placebo pts. All were mild to moderate, and each occurred in only 1 pt per cohort.
Clinical Response – Improvement in PASI Score

• Improvements in PASI scores compared to Day 1 were observed at both dosage levels, starting from Day 15 and sustained through Day 57 (five weeks after last dose).

• The pre-specified clinical endpoint of reduction in PASI scores at Day 29 was achieved in the 0.16 mg/kg cohort (p<0.02 compared to placebo), but not in the 0.32 mg/kg cohort.

• Across all PASI observations, the 0.16 mg/kg cohort was statistically different from placebo (p=0.04, repeated measures analysis). Consistent with this, plaque induration and lower limb regional PASI score were also significantly improved on Days 29, 36, and 57 for patients treated with 0.16 mg/kg compared to placebo (p<0.02 at each time point)
<table>
<thead>
<tr>
<th>Response</th>
<th>Day</th>
<th>0.16 mg/kg</th>
<th>0.32 mg/kg</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>PASI ≥35</td>
<td>29</td>
<td>5/12 (43%)</td>
<td>1/14 (7%)</td>
<td>0/14</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>5/11 (45%)</td>
<td>4/13 (31%)</td>
<td>1/14 (7%)</td>
</tr>
<tr>
<td></td>
<td>57&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7/12 (57%)</td>
<td>5/13 (38%)</td>
<td>0/12</td>
</tr>
<tr>
<td>PASI ≥50</td>
<td>57&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3/12 (25%)</td>
<td>4/13 (31%)</td>
<td>0/12</td>
</tr>
<tr>
<td>PASI ≥75</td>
<td>57</td>
<td>1/12 (6%)</td>
<td>1/13 (6%)</td>
<td>0/12</td>
</tr>
</tbody>
</table>

<sup>a</sup> p<0.005, χ², all IMO-3100 pts (12/25) vs. PLA (0/12)
<sup>b</sup> p<0.05, χ², all IMO-3100 pts (7/25) vs. PLA (0/12)
Day 1 Normal  Day 1 Lesion  Day 29 Lesion

Epidermal Thickness

K16

Epidermal CD3

Epidermal CD11c

-51%

+ to –

-65%

-81%
Biopsy Epidermal Thickness

• Skin biopsies were obtained on Days 1 and 29.
• Representative figure shows, at Day 29, K16 staining (marker of keratinocyte proliferation) reverting toward normal and decreasing infiltrates of CD3+ lymphocytes and CD11c+ mononuclear cells.
• Median change in epidermal thickness (the primary endpoint of the trial) was -6.4% in IMO-3100 pts compared to +7.7% in placebo pts (p>0.05).
• Photographs indicated that after 4 weeks of treatment the psoriatic plaques were improving unevenly. Thus, in some pts, biopsies represented residual rather than resolving disease. Similar limitations of individual biopsies have been previously reported (Ann Rheum Dis 2005;64:65-68).
DNA Microarray

- Biopsy samples from six pts treated with 0.16 mg/kg and six with placebo were analyzed by DNA microarray for expression of the MAD-3 gene set (related to the pathogenesis of psoriasis; PLoS ONE 2012;7:e44274) and of genes unique to the IL-17 pathway, a critical mechanism of immunopathology.
- The pts treated with IMO-3100 showed significant improvement compared to placebo in expression profile of both disease-associated MAD-3 genes and IL-17 pathway genes (each p<10^{-6}).
- Full data will be presented at a future meeting.
Summary

• IMO-3100, an antagonist of TLRs 7 and 9, showed therapeutic effect in multiple assessments of disease severity and mechanism in patients with moderate to severe plaque psoriasis treated for 4 weeks.

• Improvement in PASI scores were observed as soon as 2 weeks after start of treatment and were sustained up to Day 57, five weeks after the last dose (Day 22). At Day 29, the pre-defined clinical endpoint evaluation, PASI scores were significantly improved in the 0.16 mg/kg dose cohort.

• Overall, ~30% of IMO-3100 treated patients achieved PASI 50.

• Pre-defined sensitivity analyses showed significant improvement at multiple post-treatment time points in plaque induration and in lower limb regional scores.

• Plaque epidermal thickness on the Day 29 biopsy (the histologically-defined primary study endpoint) was decreased, but did not achieve statistical significance.

• DNA microarray (available on biopsies from a subset of pts) showed IMO-3100 treated pts had significant improvement in the expression profiles of MAD-3 psoriasis genes and IL-17-related genes.

• IMO-3100 was well tolerated.

• The next steps in the development of endosomal TLR antagonists are 12-week studies in psoriasis and in other autoimmune diseases.