Interleukin-17A Blockade with Secukinumab Reduces Spinal Inflammation in Patients with Ankylosing Spondylitis As Early As Week 6, As Detected by Magnetic Resonance Imaging

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Primary Clinical Endpoint: ASAS20 Response at Week 6

Secukinumab (AIN457) Induced ASAS20 Response

IL-17A: An Emerging Target in Ankylosing Spondylitis

Secukinumab, a fully human IgG1k anti-IL17A monoclonal antibody, demonstrated efficacy in proof-of-concept trials of rheumatoid arthritis, psoriasis and non-infectious uveitis1, and in phase IIb trial in rheumatoid arthritis2.

In the current proof of concept study, we explored the use of secukinumab (AIN457) for targeted IL-17A blockade as a novel therapeutic strategy in the treatment of moderate-to-severe AS.

IL-17A Selectively Impacts Pro-inflammatory Drive in Autoimmunity

Primary Clinical Endpoint: ASAS20 Response at Week 6

Greater ASAS20 Response with Secukinumab vs. Placebo

ASAS20 Response Rate (Bayesian Analysis)

<table>
<thead>
<tr>
<th>No of Responders (n)</th>
<th>Posterior mean response rate</th>
<th>Posterior mean difference in response rates (Secukinumab vs. Placebo)</th>
<th>95% credible interval</th>
<th>Probability (Secukinumab &gt; Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secukinumab</td>
<td>16/23 (69.6)</td>
<td>34.7</td>
<td>11.5 - 54.3</td>
<td>0.88</td>
</tr>
<tr>
<td>Placebo</td>
<td>1/6 (16.7)</td>
<td>34.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Background and Rationale: MRI Results in Studies with Biologics in AS

**Methods**

**Study treatment**
- Patients randomized 4:1 to receive two i.v. infusions of secukinumab 10mg/kg or placebo given 3 weeks apart in a 28-week double blind, placebo controlled study

**Study population**
- N=27 patients with active AS (1984 modified New York criteria)

**MRI assessment**
- Sagittal MRI of the spine were performed [T1 and STIR] at BL, wk 6 and wk 28
- One independent reader, blinded to treatment and chronology of images

**Statistical analysis**
- Wilcoxon signed-rank test was used for the evaluation of changes between baseline and follow-up in each treatment arm

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**Berlin MRI scoring system**

Range Berlin-Score: 0 - 69

**MRI Substudy: Demographics and Baseline Characteristics for Subgroup of Patients Who Had Evaluable MRI Studies**

<table>
<thead>
<tr>
<th>Demographics and Baseline Characteristics – MRI sub-study</th>
<th>Secukinumab (N=22)</th>
<th>Placebo (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics and Baseline Characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>12 (55)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Age (years), Mean (SD)</td>
<td>48.3 (14.3)</td>
<td>53.3 (10.0)</td>
</tr>
<tr>
<td>BMI (kg/m²), Mean (SD)</td>
<td>27.0 (5.0)</td>
<td>24.6 (5.0)</td>
</tr>
<tr>
<td>Disease duration (years), Median (range)</td>
<td>6.5 (3 – 49)</td>
<td>12 (1 – 32)</td>
</tr>
<tr>
<td>BASDAI, Mean (SD)</td>
<td>7.3 (1.4)</td>
<td>6.7 (1.4)</td>
</tr>
<tr>
<td>BASFI, Mean (SD)</td>
<td>6.4 (1.9)</td>
<td>4.6 (3.2)</td>
</tr>
<tr>
<td>BASMI, Mean (SD)</td>
<td>4.3 (1.8)</td>
<td>3.8 (1.2)</td>
</tr>
<tr>
<td>CRP (mg/L), Mean (SD)</td>
<td>7.1 (3.2 – 61.7)</td>
<td>8.4 (4.6 – 44.3)</td>
</tr>
<tr>
<td>HLA-B27 status positive n (%)</td>
<td>15 (68)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Prior TNF inhibitor use n (%)</td>
<td>9 (41)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Concomitant immunosuppressants (MTX, SSZ) n (%)</td>
<td>9 (41)</td>
<td>3 (60)</td>
</tr>
</tbody>
</table>

BMI: Body mass index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index

**MRI Substudy: Changes of MRI Scores at Week 6 Following Treatment with Secukinumab**

**MRI Substudy: Berlin MRI score at BL, Week 6 and Week 28**

**MRI scores at Baseline, Week 6 and Week 28/End of study**

<table>
<thead>
<tr>
<th>MRI scores at Baseline, Week 6 and Week 28/End of study</th>
<th>Secukinumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Mean Berlin MRI score/SD</td>
<td>9.3±2.9</td>
<td>9.7±4.4</td>
</tr>
<tr>
<td>Treatment (vs. baseline)</td>
<td>0.10</td>
<td>0.16</td>
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</tbody>
</table>

1. Data from 6 patients on secukinumab who discontinued prior to week 28 were not included; 2. Two patients on placebo discontinued prior to week 6 and instead their week 6 MRI was repeated as a week 28 assessment.
Improvement of MRI Inflammation at Week 6 and Week 28 with Secukinumab

Baseline  Week 6  Week 28

Conclusions

- This MRI substudy in patients with active AS participating in the proof-of-concept trial CAIN457A2209 showed that after treatment with only 2 infusions of secukinumab:
  - Reductions of spinal inflammation as detected by MRI
  - MRI changes were seen as early as 6 weeks after start of treatment with secukinumab, and were maintained up to Week 28
  - Results are consistent with MRI findings obtained in previous AS trials with TNF blockers
  - MRI results support the notion that the anti-IL17A mAb secukinumab may be a potential treatment for patients with active AS, consistent with results of the clinical study that met the primary endpoint
  - These results warrant further investigations in larger clinical studies