Atacicept Reduces Serum Anti-Gd-IgA1 Levels in Patients with Immunoglobulin A Nephropathy (IgAN)

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Disclosures

• Jonathan Barratt: Received consultancy payments and research funding from Vera Therapeutics
• Celia J.F. Lin: Employee of Vera Therapeutics
• Nadia Nawaz: None
• Karen Molyneux: None
• James A. Tumlin: Received consultancy payments and research funding from Vera Therapeutics
• Yusuke Suzuki: Received consultancy payments and research funding from Vera Therapeutics
Atacicept is a Dual Inhibitor (BLYS and APRIL) of Plasma Cells and B Cells

Key Considerations

- Fully humanized fusion protein, subcutaneously administered weekly
- Dual blockade by TACI-Ig shown to be more potent than blocking BLYS alone or APRIL alone and has benefit of targeting long-lived plasma cells, in addition to B cells, thus reducing autoantibody production

References:
Galactose-deficient IgA1 (Gd-IgA1) Plays a Central Role in IgAN Pathogenesis
Galactose-deficient IgA1 (Gd-IgA1) Plays a Central Role in IgAN Pathogenesis

Atacicept is the first treatment to reduce Gd-IgA1 (ERA-EDTA 2020)
Clear dose-dependent reductions on serum Gd-IgA1 with atacicept, and **atacicept 75 mg reduces Gd-IgA significantly (60%) and durably**.
Renal Survival Deteriorated by the Quartile of Serum Gd-IgA Level

- High Gd-IgA1 (Group 4) is associated with increased risk of ESRD and death\(^1\)

- Serum level of **glycan-specific IgG antibodies** is correlated with the level of urinary protein excretion\(^2\) and the risk of progression to ESRD or death\(^3\)
Elevated serum autoantibody had a worse survival rate at 5 and 10 years postdiagnosis

Cumulative Survival

Logrank test: P=0.004

N=31
Autoantibody
N=66
Yes autoantibody
Phase 2a IgAN Trial (JANUS)

Study Design

- Patients ≥18 years with IgAN
- Proteinuria (UPCR) 0.75 to 6 mg/mg
- Stable ACE inhibitor and/or ARB ≥8 weeks

IMP Treatment (1:1:1 randomization) vs Safety FU

- n ≥ 5: Placebo
- n ≥ 5: Atacicept 25mg
- n ≥ 5: Atacicept 75mg

- Interim safety review of ≥5 subjects/arm treated for ≥12 weeks; interim efficacy review after 16 subjects treated for 24 weeks
- Primary analysis at week 48 (1st endpoint: Safety)
- Final analysis at end of study
Phase 2a IgAN Trial (JANUS): Shows Compelling Proof-of-Concept in IgAN

**Change in Proteinuria by 24-hour UPCR at Week 24**

<table>
<thead>
<tr>
<th>Mean % Change from Baseline in Proteinuria (24-hr UPCR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ70.3%</td>
</tr>
<tr>
<td>+42.6%</td>
</tr>
<tr>
<td>-21.8%</td>
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<tr>
<td>-27.7%</td>
</tr>
</tbody>
</table>

**Dose-dependent reduction in UPCR at week 24**

**Median % Change from Baseline**

- IgA: 7% -13% -52% -7% -31% -38% 0% -25%
- IgG: -7% -10% -31% -7% -38% -69% -60%
- IgM: -7% -38% -69% -60%
- Gd-IgA1: 0% -25% -60%

**Dose-dependent reduction in serum IgA, IgG, and IgM**

**Atacicept also Showed Stable GFR for >1 Year vs 25% decline in Placebo**

**First molecule to show 60% reduction in Gd-IgA1 in IgAN patients**

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1. Phase 2a JANUS Trial CTR Table 13.3.3.21.
2. Phase 2a JANUS Trial CTR Table 15.3.3.9.
Phase 2a IgAN Trial (JANUS): Dose-Dependent, Durable Gd-IgA1 Reduction

Key:
- Placebo
- Atacicept 25mg
- Atacicept 75mg

Mean percent change (± SD)

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Placebo N=5</th>
<th>Atacicept 25mg N=6</th>
<th>Atacicept 75mg N=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>5</td>
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</tr>
<tr>
<td>12</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>24</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>48</td>
<td>5</td>
<td>5</td>
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</tr>
<tr>
<td>72</td>
<td>3</td>
<td>3</td>
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</table>

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In the JANUS study, serum anti-Gd-IgA1 was assessed at baseline (BL), wks 4, 12, 24, 48, and 72.

An ELISA developed using as the capture antigen an intact IgA1 paraprotein which displayed high HPA lectin binding measured Gd-IgA1-specific IgG.

Serum samples were normalized using 3 standard serum samples included on all plates.
Results

• Decrease in serum anti-Gd-IgA1 levels was observed in both atacicept 25 mg and 75 mg groups over time
• At 24 weeks, mean percent change from baseline was 24% decrease for atacicept 25 mg and 29% decrease for atacicept 75 mg
• At 72 weeks, 28% decrease for atacicept 25 mg and 39% decrease for atacicept 75 mg was observed
Percent Change from Baseline in Anti-Gd-IgA1 by Visit

![Graph showing percent change from baseline in anti-Gd-IgA1 levels by visit for Placebo, Atacicept 25mg, and Atacicept 75mg. The graph includes data points and error bars for each visit (Baseline, Week 4, Week 12, Week 24, Week 48, Week 72). The number of subjects per group per visit is also provided.]

<table>
<thead>
<tr>
<th>Visit</th>
<th>Placebo N= 5</th>
<th>Atacicept 25mg N= 6</th>
<th>Atacicept 75mg N= 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>5</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Week 4</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Week 12</td>
<td>5</td>
<td>4</td>
<td>5</td>
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<tr>
<td>Week 24</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Week 48</td>
<td>5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Week 72</td>
<td>3</td>
<td>3</td>
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</tr>
</tbody>
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Galactose-deficient IgA1 (Gd-IgA1) and Autoantibodies to Gd-IgA1 (anti-Gd-IgA1) Play a Central Role in IgAN Pathogenesis

Atacicept is the first treatment to reduce Gd-IgA1 (ERA-EDTA 2020)

Atacicept is the first treatment to reduce IgG autoantibodies to Gd-IgA1 (anti-Gd-IgA1) (ERA-EDTA 2022)
Conclusion

These results represent the first randomized controlled trial evidence to show a reduction in anti-Gd-IgA1 with an investigational therapeutic in IgAN patients.

Atacicept’s ability to decrease both circulatory Gd-IgA1 and IgG autoantibodies to this protein which are central to the pathogenesis and progression of IgAN support its potential as a disease modifying therapy for IgAN patients.

The ongoing Ph2b ORIGIN trial evaluating up to atacicept 150 mg in IgAN patients will help determine how these robust reductions in Gd-IgA1 and anti-Gd-IgA1 translate to measures of renal function, including proteinuria and GFR.
Back-up
Phase 2a IgAN Trial (JANUS): Clear Dose-Dependent Reductions on Serum Igs