36-Week Efficacy & Safety of Atacicept 150 mg in the ORIGIN Randomized, Double-blind, Placebo-controlled Phase 2b Study in IgAN and Persistent Proteinuria

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Late Breaking Clinical Trial
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Disclosure of Interest for Richard Lafayette

- Consultant for Vera, Omeros, Calliditas, Chinook, Alexion, Otsuka, Novartis, GSK, Alnylam
- Employee of Stanford University Medical Center, which has received research funding from Vera, Omeros, ChemoCentryx, Chinook, Alexion, Otsuka, Calliditas, Roche, NIH, and University of Michigan

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Atacicept: Dual Inhibitor (BLyS/APRIL) of B Cells and Plasma Cells with Potential to Address Multiple Autoimmune Diseases

- Fully humanized TACI-Ig fusion protein, subcutaneously administered
- Low nanomolar potency vs BLyS (Kd 1.45 nM) and APRIL (Kd 0.672 nM)
- Reduces overstimulation of B cells and plasma cells\(^1\) and autoantibody production\(^2\)
- Dual inhibition more potent than either alone\(^3\), may translate to more sustained B cell modulation
- Well-characterized safety profile with exposure in >1500 patients across different indications\(^4\)

APRIL = a proliferation-inducing ligand; BLyS = B lymphocyte stimulator; TACI = transmembrane activator and CAML interactor. 
Atacicept is investigational and has not been approved by any regulatory authorities.
Atacicept Targets Upstream Hits of IgAN Pathogenesis


1. B cell priming
2. Plasma cell mistrafficking to the systemic circulation
3. Atacicept reduces Gd-IgA1
4. Atacicept reduces anti-Gd-IgA1 antibodies
5. Atacicept reduces immune complexes
6. Gd-IgA1-containing immune complexes deposit in glomeruli
7. Progressive renal injury

Steps that Atacicept targets


ORIGIN Phase 2b IgAN Trial: Study Design and Objectives

Multinational, randomized, placebo-controlled trial

- **Placebo**  
  n=30
- **Atacicept 25 mg qwk**  
  n=15
- **Atacicept 75 mg qwk**  
  n=30
- **Atacicept 150 mg qwk**  
  n=30

**Endpoints**

- Primary efficacy: UPCR-24h at week 24 ★
- Key secondary: UPCR-24h at week 36 ★
- eGFR change up to week 96 ★
- Gd-IgA1 change
- Safety

**Inclusion Criteria**

- Patients ≥18 years old with IgAN on renal biopsy and high risk of disease progression
- Stable and optimized RAASi for 12 weeks
- Use of SGLT2i allowed
- UPCR-24h >0.75 g/g or UP >0.75 g per 24h
- eGFR ≥30 mL/min/1.73 m²
- Blood pressure ≤150/90 mmHg

**Endpoints**

- Primary efficacy: UPCR-24h at week 24 ★
- Key secondary: UPCR-24h at week 36 ★
- eGFR change up to week 96 ★
- Gd-IgA1 change
- Safety

eGFR = estimated glomerular filtration rate; ET = end of treatment; RAASi = renin-angiotensin-aldosterone system inhibitor; SGLT2i = sodium-glucose cotransporter-2 inhibitor; UPCR = urine protein:creatinine.
Patient Disposition

Screened, n=232

Screen Failures, n=116

Randomized and Treated, n=116

All Atacicept, n=82

n=82

n=73 (89%)

Completed Week 36 and entered OLE

n=80 (98%)

Discontinued
n=2 (2%)\(^1\)

Safety and ITT population

Prespecified Week 36 PP analysis

Excludes patients with protocol violations as identified by blinded third-party CRO

Placebo, n=34

n=34

n=26 (76%)

Discontinued
n=3 (9%)\(^2\)

Completed Week 36 and entered OLE

n=31 (91%)

Safety data includes all post-week 36 visits available at data-cut March 09, 2023. ITT = intent to treat; PP = per protocol; OLE = open label extension.

1. Discontinued to pursue elective surgery (1), discontinued due to positive hepatitis B DNA and adverse event (1).
2. Initiated prohibited medication for concomitant disease (1), discontinued due to plan to start prohibited medication for concomitant disease (1) and adverse event (1).
## Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Mean ± SD or n (%)</th>
<th>Overall n=116</th>
<th>Atacicept 25 mg n=16</th>
<th>Atacicept 75 mg n=33</th>
<th>Atacicept 150 mg n=33</th>
<th>Placebo n=34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>39 ± 12.6</td>
<td>40 ± 15.0</td>
<td>41 ± 12.6</td>
<td>38 ± 11.4</td>
<td>39 ± 13.0</td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>69 (59)</td>
<td>9 (56)</td>
<td>19 (58)</td>
<td>22 (67)</td>
<td>19 (56)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>62 (53)</td>
<td>7 (44)</td>
<td>12 (36)</td>
<td>17 (52)</td>
<td>26 (76)</td>
</tr>
<tr>
<td>Asian</td>
<td>51 (44)</td>
<td>7 (44)</td>
<td>20 (61)</td>
<td>16 (48)</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (3)</td>
<td>2 (12)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>63 ± 27.3</td>
<td>71 ± 28.7</td>
<td>64 ± 25.4</td>
<td>56 ± 22.7</td>
<td>66 ± 31.7</td>
</tr>
<tr>
<td>UPCR by 24h urine, g/g</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>1.6 ± 0.9</td>
<td>1.6 ± 0.8</td>
<td>1.7 ± 0.9</td>
<td>1.7 ± 1.0</td>
<td>1.6 ± 0.8</td>
</tr>
<tr>
<td>SGLT2i use</td>
<td>16 (14)</td>
<td>3 (19)</td>
<td>3 (9)</td>
<td>4 (12)</td>
<td>6 (18)</td>
</tr>
</tbody>
</table>
UPCR % Change with Atacicept 150 mg at Week 36

ITT Analysis

Placebo
n=34

Atacicept 150 mg
n=33

-33%

Δ 35%
p=0.012

PP Analysis

Placebo
n=26

Atacicept 150 mg
n=26

-40%

Δ 43%
p=0.003

p-values, percentage changes from baseline, and treatment differences were computed using FDA-endorsed mixed-effects modeling which takes into account the effects of baseline UPCR and eGFR.

1. PP analysis excludes patients with protocol violations identified at week 36 data-cut prior to unblinding.
eGFR Change with Atacicept 150 mg Through Week 36

ITT analysis; p-values, percentage changes from baseline, and treatment differences were computed using FDA-endorsed mixed-effects modeling.

Mean ± SE % Change from Baseline in eGFR

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo</th>
<th>Atacicept 150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>12</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>24</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>36</td>
<td>30</td>
<td>31</td>
</tr>
</tbody>
</table>

-8.5% - 1.6% Δ 11% p=0.038

5.8 mL/min/1.73 m²
Absolute difference in mean change at week 36
Dose-dependent Reductions Observed in Serum IgG, IgA, and IgM Through Week 36

ITT analysis; *p<0.001. p-values, percentage changes from baseline, and treatment differences were computed using FDA-endorsed mixed-effects modeling.

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo</th>
<th>Atacicept 25 mg</th>
<th>Atacicept 75 mg</th>
<th>Atacicept 150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>34</td>
<td>16</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>16</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>12</td>
<td>34</td>
<td>16</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>24</td>
<td>34</td>
<td>16</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>36</td>
<td>30</td>
<td>15</td>
<td>33</td>
<td>30</td>
</tr>
</tbody>
</table>

Mean ± SE % Change from Baseline

- IgG: 0% ± 0%, -14% ± 0%, -32% ± 0%, -37% ± 0%
- IgA: 0% ± 0%, -4% ± 0%, -32% ± 0%
- IgM: 0% ± 0%, -3% ± 0%, -59% ± 0%, -70% ± 0%, -73% ± 0%
Gd-IgA1 % Change Through Week 36

Mean ± SE % Change from Baseline in Gd-IgA1

Week

0 4 12 24 36

Placebo 33 33 33 33 29
Atacicept 25 mg 16 16 16 15 15
Atacicept 75 mg 33 33 33 33 33
Atacicept 150 mg 32 32 30 30 30

n=

ITT analysis; *p<0.001 vs placebo. p-values, percentage changes from baseline, and treatment differences were computed using FDA-endorsed mixed-effects modeling.
## Treatment-Emergent Adverse Events Through Week 36

### Table: Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Atacicept 25 mg n=16</th>
<th>Atacicept 75 mg n=33</th>
<th>Atacicept 150 mg n=33</th>
<th>Placebo n=34</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAEs</td>
<td>11 (69)</td>
<td>24 (73)</td>
<td>25 (76)</td>
<td>27 (79)</td>
</tr>
<tr>
<td>Study drug-related TEAEs&lt;sup&gt;1&lt;/sup&gt;</td>
<td>6 (38)</td>
<td>17 (52)</td>
<td>19 (58)</td>
<td>14 (41)</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>0</td>
<td>1 (3)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1 (3)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>3 (9)&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>TEAEs leading to study drug discontinuation</td>
<td>0</td>
<td>0</td>
<td>1 (3)&lt;sup&gt;5&lt;/sup&gt;</td>
<td>1 (3)&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- No patient had study drug discontinuation or interruption due to low IgG (hypogammaglobulinemia)

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1. Majority of study drug-related TEAEs were injection site reactions; one contributed to drug discontinuation.
2. Multiple fractures, resolved, unrelated to study treatment.
4. Anaphylactic reaction resolved (n=1); forearm fracture resolved (n=1); flank pain not resolved and ulnar nerve paralysis resolved with sequelae (n=1); all unrelated to study treatment.
5. Discontinued after 3 injections due to injection site reaction and positive hepatitis B DNA that resolved without treatment 3 weeks later, normal liver function throughout.
6. Discontinued after 31 injections due to worsening flank pain that was not resolved; unrelated to study treatment.
Infections Were Balanced Between Atacicept and Placebo Through Week 36

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Atacicept 25 mg n=16</th>
<th>Atacicept 75 mg n=33</th>
<th>Atacicept 150 mg n=33</th>
<th>Placebo n=34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections¹</td>
<td>6 (38)</td>
<td>16 (48)</td>
<td>13 (39)</td>
<td>11 (32)</td>
</tr>
<tr>
<td>Occurring in &gt;1 patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COVID-19</td>
<td>4 (25)</td>
<td>9 (27)</td>
<td>8 (24)</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0</td>
<td>3 (9)</td>
<td>2 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0</td>
<td>1 (3)</td>
<td>3 (9)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (13)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Viral infection</td>
<td>0</td>
<td>2 (6)</td>
<td>0</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Influenza</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>1 (6)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

¹. One severe infection (gastroenteritis norovirus, resolved and not related to study treatment); all others were mild or moderate.
Conclusions

• The Phase 2b trial met its primary endpoint of significant proteinuria reduction at week 24 in IgAN patients at high risk of disease progression

• At week 36, patients receiving atacicept 150 mg had a statistically significant 43% reduction in proteinuria compared to placebo

• Patients receiving atacicept had stable eGFR through week 36, demonstrating a statistically significant and clinically meaningful difference of 5.8 mL/min/1.73 m² compared to placebo at week 36

• Clinical safety profile was similar between atacicept and placebo

• A confirmatory Phase 3 (ORIGIN 3) trial evaluating self-administered atacicept 150 mg SC qwk (1 mL) vs placebo is currently enrolling
Thank you to all our ORIGIN Phase 2b study volunteers and the ORIGIN investigators and study staff.