Long-Term Phase 2 Efficacy of the MASP-2 Inhibitor Narsoplimab for Treatment of Severe IgA Nephropathy

Richard A. Lafayette MD, Stanford University, Stanford, CA, USA
Kevin Carroll PhD, KJC Statistics Ltd, Cheshire, UK
Jonathan Barratt PhD FRCP, University of Leicester, Leicester, UK
Disclosures

**RL**: Consultant – Omeros Corporation  
**KC**: Consultant – Omeros Corporation  
**JB**: Consultant – Omeros Corporation

**Support**: This study was sponsored by Omeros Corporation, Seattle, WA.

**Acknowledgements**: Medical writing support was provided by Jonathan Latham of PharmaScribe, LLC, and funded by Omeros Corporation, Seattle, WA.

Narsoplimab is an investigational agent and has not been approved by any regulatory agency.
Narsoplimab Inhibits MASP-2, the Effector Enzyme of the Lectin Pathway, Which is Activated in IgAN

**Activation of the lectin pathway contributes to tubular and podocyte damage in IgAN**

- Circulating galactose-deficient IgA antibodies (GdIgA)
- Immune complexes form containing MBL/MASP-2 complexes and anti-glycan antibodies bound to GdIgA
- Immune complexes deposit on mesangial cells, Lectin pathway of complement is activated
- Pro-inflammatory, pro-fibrotic cytokine production
- Pro-inflammatory, pro-fibrotic cytokine production
- Mesangial cell proliferation
- Tubular damage and proteinuria
- Local upregulation of CL-11, a LP recognition molecule, leads to a cycle of increasing inflammation/proteinuria

**Narsoplimab inhibits MASP-2, the effector enzyme of the lectin pathway**

**CLASSICAL PATHWAY**
- Immune complex
- C1q
- C1r/C1s
- C4
- C2
- C3 convertase
- C4 bypass

**LECTIN PATHWAY**
- MBL, ficolins, collectins
- MBL
- MASP-2
- Factor XII
- Factor Xlla
- Prothrombin
- Thrombin

**ALTERNATIVE PATHWAY**
- Factor B
- Factor D
- pro-Factor D
- MASP-3
- Terminal Pathway (C5b-9)
- C5
- C5a
- C5b
- C6-9
- MACH
- Cell lysis

**Inflammation, platelet activation, leukocyte recruitment, endothelial cell activation**

**PROGRESSIVE RENAL DYSFUNCTION**

- Podocyte damage and hematuria
- Cell lysis


CL-11, collectin-11; IgAN, IgA nephropathy; LP, lectin pathway; MAC, membrane attack complex; MASP, mannan-binding lectin-associated serine protease; MBL, mannan-binding lectin.
Staged Phase 2 Study of Narsoplimab in Adult Patients with Severe IgAN (NCT02682407)

**Key inclusion criteria:**
- Adults with severe IgAN
- UPE >1 g/d
- eGFR ≥30 mL/min/1.73 m$^2$

**Primary endpoint**
- Safety and tolerability of narsoplimab

**Key secondary endpoints**
- 24-hour UPE and eGFR, assessed by time-weighted average regression analysis

**Substudy 1: Open-Label (steroid taper during study)**
- Narsoplimab 4 mg/kg IV weekly x12 weeks (n = 4) → 6 wks of follow-up → Open-label treatment* and follow-up for up to 35 months total (n = 4)

**Substudy 2: Double-Blind (no steroid use at baseline)**
- Randomized (n = 12)
  - Narsoplimab 370 mg IV weekly x12 weeks (n = 6) → 6 wks of follow-up (n = 5)
  - Vehicle IV weekly x12 weeks (n = 6) → 6 wks of follow-up (n = 3) → Open-label treatment* and follow-up for up to 35 months total (n = 8)

*Open-label narsoplimab 370 mg IV weekly x12 weeks could be administered if UPE was >1 g/d (or ≥50% of baseline)

eGFR, estimated glomerular filtration rate; IgAN, IgA nephropathy; IV, intravenous; UPE, urine protein excretion.
Twelve Patients Were Treated and Followed for up to 35 Months (Median, 22 Months)

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>n (%) or median [range] (N = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>35 [24 – 60]</td>
</tr>
<tr>
<td>Male</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>White</td>
<td>11 (92%)</td>
</tr>
<tr>
<td>Time since IgAN diagnosis, y</td>
<td>6.9 [0.4 – 27.5]</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>40.7 [25.4 – 75.9]</td>
</tr>
<tr>
<td>UPE, g/d</td>
<td>4.2 [1.5 – 11.9]</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (83%)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>127 [101 – 162]</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>84 [60 – 104]</td>
</tr>
<tr>
<td>Obesity</td>
<td>7 (58%)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>32.5 [24.4 – 44.3]</td>
</tr>
</tbody>
</table>

Narsoplimab treatment (1 course = 12 weekly IV doses)
- Median, 1 course per year (range, 0.7–2.5)
- 7 patients (58%) received 1 course or less per year

eGFR, estimated glomerular filtration rate; IgAN, IgA nephropathy; IV, intravenous; UPE, urine protein excretion.
Narsoplimab Treatment Decreased the Rate of Decline in eGFR Relative to External Comparator Group

Narsoplimab annualized rate of decline (SE) = 5.2 (2.1) mL/min/yr
Comparator* annualized rate of decline (SE) = 8.6 (3.7) mL/min/yr

* Comparator: patients from Leicester Renal Unit IgA Nephropathy Registry with similar disease burden and matched baseline UPE and eGFR values

eGFR, estimated glomerular filtration rate; SE, standard error; UPE, urine protein excretion.
eGFR Increased in 3/12 Patients and Remained Stable for Others

eGFR, estimated glomerular filtration rate.

- eGFR Analysis Value
- Regression line
- 12-week courses of narsoplimab treatment
Estimated Mean UPE Decrease was 38% From Baseline Through ~3 Years

Regression line corresponds to an average baseline UPE of 3.8 g/d (SD, 2.4) at initiation of narsoplimab treatment

Baseline slope (SE), −0.36068 (0.13606); time slope (SE), −0.62664 (0.36902)

10 of 12 patients had improvement of UPE from baseline

UPE, urine protein excretion.
## No Subject Had a Treatment-Related Serious Adverse Event

<table>
<thead>
<tr>
<th>Treatment-Emergent Adverse Event</th>
<th>Substudy 1 (N = 4) n (%)</th>
<th>Substudy 2 (N = 8) n (%)</th>
<th>Total (N = 12) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>3 (75)</td>
<td>1 (13)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2 (50)</td>
<td>2 (25)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (25)</td>
<td>1 (13)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>0</td>
<td>2 (25)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>2 (50)</td>
<td>0</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1 (25)</td>
<td>1 (13)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Gout</td>
<td>0</td>
<td>2 (25)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (50)</td>
<td>0</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Ligament sprain</td>
<td>0</td>
<td>2 (25)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>0</td>
<td>2 (25)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>1 (25)</td>
<td>1 (13)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1 (25)</td>
<td>1 (13)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (25)</td>
<td>1 (13)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Toothache</td>
<td>1 (25)</td>
<td>1 (13)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0</td>
<td>2 (25)</td>
<td>2 (17)</td>
</tr>
</tbody>
</table>

Table includes adverse events that occurred in at least 2 patients.
In this phase 2 study, adults with severe IgAN receiving narsoplimab treatment were followed for ~3 years

Narsoplimab treatment improved, stabilized, or markedly slowed decline of eGFR (versus external comparator)

- While other studies reported 1-year follow-up data in patients with IgAN, this is the first study to show sustained stabilization – or improvement – of eGFR with longer-term follow-up

Narsoplimab treatment resulted in a mean decrease of 38% in UPE from baseline through ~3 years

Treatment was well tolerated, with no treatment-related serious adverse events

These results support further investigation of narsoplimab treatment in patients with IgAN

- The ARTEMIS-IGAN phase 3 clinical trial of narsoplimab for IgAN is currently enrolling (NCT03608033)

eGFR, estimated glomerular filtration rate; IgAN, IgA nephropathy; UPE, urine protein excretion.