Broadening Narsoplimab Development from Orphan Indication to COVID-19 Treatment: CMC Regulatory Considerations

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Outline

- Omeros Corporation
- Introduction to narsoplimab and regulatory status
- Clinical data summaries
  - HCST-TMA
  - COVID-19
- Narsoplimab CMC development
- CMC challenges and regulatory considerations for adding COVID-19 as a treatment indication to an orphan drug
Seattle-based with additional research institute at University of Cambridge

~300 employees; fully vertically integrated

1 product approved in US and EU - O MIDRI A®

BLA under priority review for narsoplimab to treat HSCT-TMA; MAA in preparation - expected to be first drug approved for this indication

Deep pipeline of innovative products targeting serious and life-threatening indications including:

- COVID-19-related ARDS
- Renal diseases
- Ischemia-reperfusion injury (e.g., stroke, MI)
- Addiction and other CNS disorders
- Immuno-oncology

Experienced internal discovery, development, and commercial functions

Publicly traded on Nasdaq (OMER)
Narsoplimab and Regulatory Status

- Narsoplimab is a fully human IgG4 antibody against mannan-binding lectin-associated serine protease-2 (MASP-2), the effector enzyme of the lectin pathway of complement
- Completed pivotal clinical program in hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA)
- BLA for HSCT-TMA under priority review at FDA
- Enrolling 2 additional Phase 3 clinical programs - IgA nephropathy (IgAN) and atypical hemolytic uremic syndrome (aHUS)
- Over 250 patients and healthy volunteers have been dosed with narsoplimab
- No significant safety concerns have been observed
- FDA has granted narsoplimab Breakthrough Therapy designation in both HSCT-TMA and IgAN (both also have orphan drug status)
- Broad therapeutic areas for lectin pathway inhibition:
  - Endothelial injury syndromes (EIS)
  - Proteinuric diseases
  - Ischemia-reperfusion injury
Narsoplimab is a Potential Therapeutic for a Broad Range of Disorders, Including HSCT-TMA and COVID-19

LECTIN PATHWAY

Tissue injury

MBL, ficolins, collectins

Factor XII

Factor XIIa

Prothrombin

Thrombin

Coagulation

ALTERNATIVE PATHWAY

Factor B

Factor D

pro-Factor D

MASP-2

C4 bypass

C5 convertases

C3 convertase

C1q

Immune complex

CLL

aGVHD

CLS

DAH

IPS

SOS/VOD

HELLP/CAPS

By blocking MASP-2, narsoplimab inhibits activation of the lectin pathway

LECTIN PATHWAY Disorders

- COVID-19
- HSCT and TMA-related EIS
  - aGVHD
  - CLS
  - DAH
  - IPS
  - SOS/VOD
  - HELLP/CAPS
- Oncology
  - Colorectal Cancer
  - Cervical Cancer
  - ESCC
- Acute transplant & surgery-related conditions
  - Delayed Graft Function (solid organ transplant)
- Chronic nephrology/proteinuria diseases
  - IgAN
  - MGN
  - Lupus Nephritis

CLASSICAL PATHWAY

Immune complex

C1q

C1r/C1s

C3a

C3b

C5a

C5b

C6-9

MAC

Cell lysis

Inflammation, platelet activation, leukocyte recruitment, endothelial cell activation

Coagulation

By blocking MASP-2, narsoplimab inhibits activation of the lectin pathway
Narsoplimab Targets MASP-2 and the Lectin Pathway of Complement

- Fully human monoclonal antibody
- Binds to MASP-2, the effector enzyme of the lectin pathway of complement
- Leaves intact the effector function of the adaptive immune response, important for fighting infection
- Blocks MASP-2-mediated coagulation (conversion of prothrombin to thrombin and activation of Factor XII to XIIa) and activation of kallikrein
- Only agent that targets MASP-2 and blocks the lectin pathway

Narsoplimab in Hematopoietic Stem Cell Transplant-Associated Thrombotic Microangiopathy
HSCT-TMA: A Serious and Potentially Fatal Complication of HSCT Caused by Endothelial Injury

25,000 - 30,000 annual allogeneic HSCT in the US and EU

No approved therapies for HSCT-TMA

~40% incidence of TMA in allogeneic HSCT

Up to 80% of patients with HSCT-TMA display at least one high-risk feature

~90% or more of severe cases of HSCT-TMA can be fatal
Study Population

- Single-arm, open-label study of high-risk HSCT-TMA patients
- Protocol specified that patients receive narsoplimab once weekly for ≥ 4 weeks
- 93% of the trial population had multiple risk factors for poor outcomes

Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>N=28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean &amp; median age (years)</td>
<td>48</td>
</tr>
<tr>
<td>Male Gender, n (%)</td>
<td>20 (71.4%)</td>
</tr>
<tr>
<td>Malignant underlying disease</td>
<td>27 (96.4%)</td>
</tr>
<tr>
<td>Risk factors:</td>
<td></td>
</tr>
<tr>
<td>Presence of GVHD, n (%)</td>
<td>19 (67.9%)</td>
</tr>
<tr>
<td>Significant infection, n (%)</td>
<td>24 (85.7%)</td>
</tr>
<tr>
<td>Pulmonary dysfunction (%)</td>
<td>5 (17.9%)</td>
</tr>
<tr>
<td>Neurological dysfunction, n (%)</td>
<td>16 (57.1%)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>21 (75.0%)</td>
</tr>
<tr>
<td>Multi-organ involvement, n (%)</td>
<td>14 (50.0%)</td>
</tr>
</tbody>
</table>

Efficacy Measures

- **Primary Endpoint**: Response as assessed by clinically meaningful improvement in TMA laboratory markers and organ function
  
  - 15% complete response rate is the FDA-agreed threshold for primary endpoint
- **Secondary Endpoints**: 100-day survival and change from baseline in TMA lab measures
All treated patients (N=28) (95% CI)

61%
(17/28)
(40.6% to 78.5%)
p<0.0001*

Patients treated per protocol (≥ 4 weeks of dosing) (n=23) (95% CI)

74%
(17/23)
(51.6% to 89.8%)
p<0.0001*

* Exact two-sided p-value for testing response rate equal to 15%

15% is the FDA-agreed efficacy threshold for the primary endpoint (i.e., the complete response rate) in the clinical trial
100-Day Survival Following HSCT-TMA Diagnosis

- All treated patients (N=28): 68% (19/28)
- Patients treated per protocol (≥ 4 weeks of dosing) (n=23): 83% (19/23)
- Complete responders (n=17): 94% (16/17)
Median survival for the full analysis population was 274 days
(95% CI) (103, NE)

Median survival for the per-protocol population was 361 days
(95% CI) (176, NE)

Median survival for the responder population was not estimable
(95% CI) (273, NE)

Median survival is estimated by Kaplan-Meier method. 95% confidence interval for median survival is calculated using complementary log-log transformation.
Narsoplimab was well tolerated in this very sick population with multiple comorbidities.

The most commonly reported adverse events were nausea, vomiting, diarrhea, hypokalemia, neutropenia and fever.

The observed adverse events are comparable to those typically seen in the post-transplant population.

6 patients died during the trial due to causes common in HSCT.

### Preferred Term, n (%) (N = 28)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Event</td>
<td>27 (96.4)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10 (35.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (32.1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (32.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (25.0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7 (25.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>Back pain</td>
<td>5 (17.9)</td>
</tr>
</tbody>
</table>
Narsoplimab for the Treatment of COVID-19-Related ARDS Requiring Mechanical Ventilation
Role of Endothelial Injury in COVID-19 Published Across Numerous Peer-reviewed Journals
Endothelial Injury with Complement Activation is Central to Pathophysiology of HSCT-TMA and COVID-19

- Once endothelial injury occurs, pathophysiology of HSCT-TMA and COVID-19 are similar
- Endothelial injury activates the lectin pathway of complement
- In HSCT-TMA, endothelial injury is caused by conditioning regimen, immunosuppressants, GVHD and infection
- In COVID-19, endothelial injury is caused by direct viral infection
- MASP-2, the lectin pathway’s effector enzyme, is bound by the nucleocapsid and spike proteins of SARS-CoV-2, activating the lectin pathway that leads to amplification of underlying cellular injury and induces cytokine response
- Viral load has no correlation in COVID-19 patients to clinical status or disease severity

**Components of COVID-19:**
- Complement activation
- Inflammation
- Coagulation

Narsoplimab inhibits all 3
## Parallels Between COVID-19 and HSCT-TMA

<table>
<thead>
<tr>
<th>Comparator</th>
<th>COVID-19</th>
<th>HSCT-TMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lectin-Pathway Activation from Endothelial Damage</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cause of Endothelial Injury</td>
<td>Viral</td>
<td>Conditioning regimen, Immunosuppressants, GVHD, infection</td>
</tr>
<tr>
<td>MASP-2 Activation</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Multi-Organ TMA</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

- ~70 patients have been dosed with narsoplimab across the two endothelial injury syndromes
- Marked improvement was noted in narsoplimab-treated patients in these studies
### Demographics and Treatment Summary

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Median (range) or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>57 years (47-63)</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td>5 (83%)</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>86 Kg (82-100 Kg)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetes (n=1); Hypertension (n=1); Dyslipidemia (n=2); Obese/Overweight (n=6)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Summary</th>
<th>n (%) or Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing of narsoplimab treatment from start of CPAP oxygen support</strong></td>
<td></td>
</tr>
<tr>
<td>Within 24 hours</td>
<td>4 (67%)</td>
</tr>
<tr>
<td>Within 48 hours</td>
<td>2 (33%)</td>
</tr>
<tr>
<td>Time from hospital admission to treatment</td>
<td>2 days (1-4)</td>
</tr>
<tr>
<td>Duration of follow-up (to date) after first dose</td>
<td>27 days (16-90)</td>
</tr>
</tbody>
</table>

All patients recovered, survived and were discharged - 2 retrospective control groups with similar entry criteria and baseline characteristics had mortality rates of 32% and 53%

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Evidence of Endothelial Damage (CEC Counts) in COVID-19

5 normal (uninfected) and 33 infected patients without Narsoplimab

IL-6 / IL-8 Levels Improved in all 6 Patients Treated with Narsoplimab

6 infected patients treated with Narsoplimab
Data from Cohort 1 of the COVID-19 Study in Italy

C-Reactive Protein
Improved in all 6 Patients

Spearman correlation = -0.83, p < 0.0001

Lactate Dehydrogenase
Improved in all 6 Patients

Spearman correlation = -0.37, p = 0.005

Aspartate Aminotransferase (AST)
Improved in all 6 Patients

Spearman correlation = -0.55, p < 0.0001

D-Dimer
Improved in all Assessed Patients
At 5-6 Month Follow-Up, All Cohort 1 Patients Showed No Clinical or Laboratory Evidence of Sequelae

<table>
<thead>
<tr>
<th>Laboratory Findings</th>
<th>Baseline</th>
<th>Last Evaluation (5-6 Mos. Post-Discharge)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cell count - per mm$^3$, median (range)</td>
<td>8335 (6420-10,120)</td>
<td>7320 (3200-8770)</td>
</tr>
<tr>
<td>&gt; 10,000 per mm$^3$ - no. (%)</td>
<td>2 (33)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>&lt; 4000 per mm$^3$ - no. (%)</td>
<td>0 (0)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Lymphocyte count - per mm$^3$, median (range)</td>
<td>875 (410-1290)</td>
<td>2815 (810-3780)</td>
</tr>
<tr>
<td>Platelet count - x 10$^3$ per mm$^3$, median (range)</td>
<td>282 (199 -390)</td>
<td>238 (170-354)</td>
</tr>
<tr>
<td>Hemoglobin - g/dL, median (range)</td>
<td>13.4 (13.2-14.1)</td>
<td>14.8 (13.4-15.8)</td>
</tr>
</tbody>
</table>

Distribution of other findings (laboratory reference ranges)

| C-reactive protein (0.0-1.0 mg/dL)                | 14 (9.5-31.3)             | 0.15 (0-0.5)                             |
| Lactate dehydrogenase (120/246 U/L)             | 518.5 (238-841)           | 212 (119-249)                           |
| Aspartate aminotransferase (13-40 U/L)          | 78.5 (51-141)             | 18 (12-29)                               |
| Alanine aminotransferase (7-40 U/L)             | 73 (37-183)               | 22.5 (20-67)                            |
| Creatinine (0.3-1.3 mg/dL)                      | 0.85 (0.38-1.33)          | 0.94 (0.51-1.07)                        |
| D-dimer (< 500 ng/mL)                           |                          |                                         |
| < 190 - no. (%)                                 | 0 (0)                    | 3 (50)                                   |
| > 190 - median (range)                          | 1250.5 (943-1454)        | 324 (202-390)                           |

Clinical status at last evaluation of all 6 patients - no evidence of COVID sequelae
Additional Cohorts of COVID-19 Patients Treated with Narsoplimab

- Have continued treating patients in the US and in Bergamo under compassionate use
  - All additional patients have been severely ill prior to treatment with narsoplimab
  - All intubated with majority initiating narsoplimab multiple days after intubation
  - All had failed other therapies prior to initiating narsoplimab

- Similarly striking outcomes to those in the initial Bergamo study, published in peer-reviewed journal Immunobiology
Summary of Narsoplimab Treatment in Seriously Ill COVID-19 Patients

- Critically ill COVID-19 and HSCT-TMA patients share the same pathophysiology - both are endothelial injury syndromes
- Narsoplimab has been used to treat ~70 seriously ill COVID-19 and HSCT-TMA patients with striking results
- All COVID-19 patients treated with narsoplimab had ARDS requiring mechanical ventilation
- All patients had high-risk characteristics/comorbidities
- Most COVID-19 patients showed rapid and marked improvement in symptoms and laboratory values and were subsequently discharged from the hospital
- Narsoplimab-treated COVID-19 patients for whom follow-up (5-6 month) data are available show no observed clinical or laboratory evidence of longer-term sequelae
Current Status and Ongoing Activities

- Recently became part of the I-SPY COVID-19 TRIAL: An Adaptive Platform Trial for Critically Ill Patients
- Advancing discussions with BARDA, NIAID, NCATS, and the Biden-Harris Transition COVID-19 Advisory Board
- In discussions with international regulatory authorities
Narsoplimab Chemistry, Manufacturing, and Controls
Narsoplimab CMC Status

- Narsoplimab CMC development assumed initial approvals for orphan indications
  - Small-scale manufacturing processes
- Cell culture process and purification steps typical for CHO cell antibody product
- Drug product is standard aseptic liquid fill for IV administration
- No unusual Critical Quality Attributes for monoclonal Ab
- Potency assay applicable to all current indications, including COVID-19
  - Bind MASP-2 to block the lectin pathway
- Straightforward control strategy
- Supply chain — all well-established contract manufacturers and labs with positive FDA inspection histories
  - DS and DP manufacturing outside US
  - Multiple QC testing locations
Narsoplimab CMC Challenges for COVID-19 Development and Regulatory Considerations
Narsoplimab CMC Challenges adding COVID-19 to an Orphan Drug Program

- **Product supply**
  - Ongoing global clinical studies in TMA, IgAN, aHUS
  - Preparation for commercial HSCT-TMA launch
  - COVID-19 (Clinical trials and potential EUA)

- **Supply chain**
  - Omeros competing with other sponsors for DS and DP capacity at CMOs
  - Multiple QC testing locations – capacity and coordination
  - Need to factor in lead times for testing and release activities ahead of internal cGMP record and data review
  - DS and DP manufactured ex-US
    - International shipping logistics adds time
    - Travel restrictions for person-in-plant
Narsoplimab CMC Challenges adding COVID-19 to an Orphan Drug Program

- Narsoplimab BLA is a breakthrough therapy designated product in Priority Review (shortened review clock)
  - FDA Information Requests
  - Inspections
- At current stage of development, narsoplimab does not have commercial historical CMC data that could help optimize plans and inform setting appropriate acceptance criteria for scale-up and facility transfers
What is the right CMC strategy for timely scale-up and additional manufacturing facilities given the urgency of COVID-19?

- During a pandemic can any regulatory requirements be adjusted while maintaining product quality and ensuring patient safety?
  - Are there possible innovative approaches to Process Validation?
  - Are simultaneous comparability studies (for example multiple facility changes) feasible?
  - What is the minimum amount of stability data required?

- Can tech transfer be streamlined?

- How are products prioritized at manufacturing facilities where there is more than one for COVID-19 being produced?
  - Manufacturing slots
  - Lead times for supply of reagents and materials