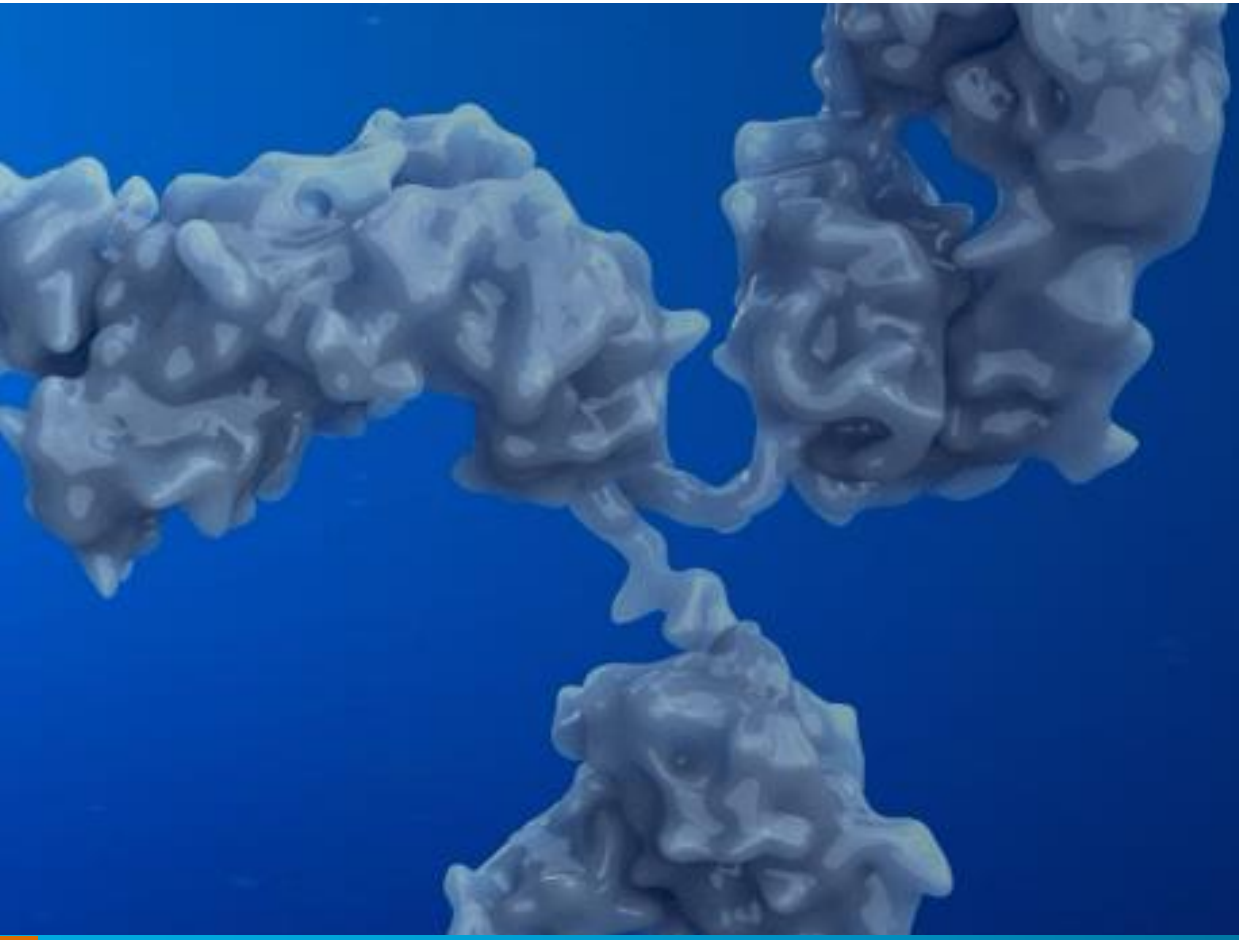

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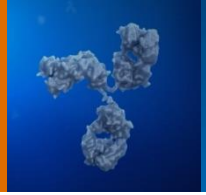
Broadening Narsoplimab Development from Orphan Indication to COVID-19 Treatment: CMC Regulatory Considerations

Jonathan Harris
Omeros Corporation
Sr. Director, Regulatory Affairs CMC
February 2, 2021



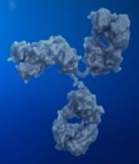
Outline

- 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

Omeros Corporation

- Seattle-based with additional research institute at University of Cambridge
- ~300 employees; fully vertically integrated
- 1 product approved in US and EU – OMIDRIA®
- 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)

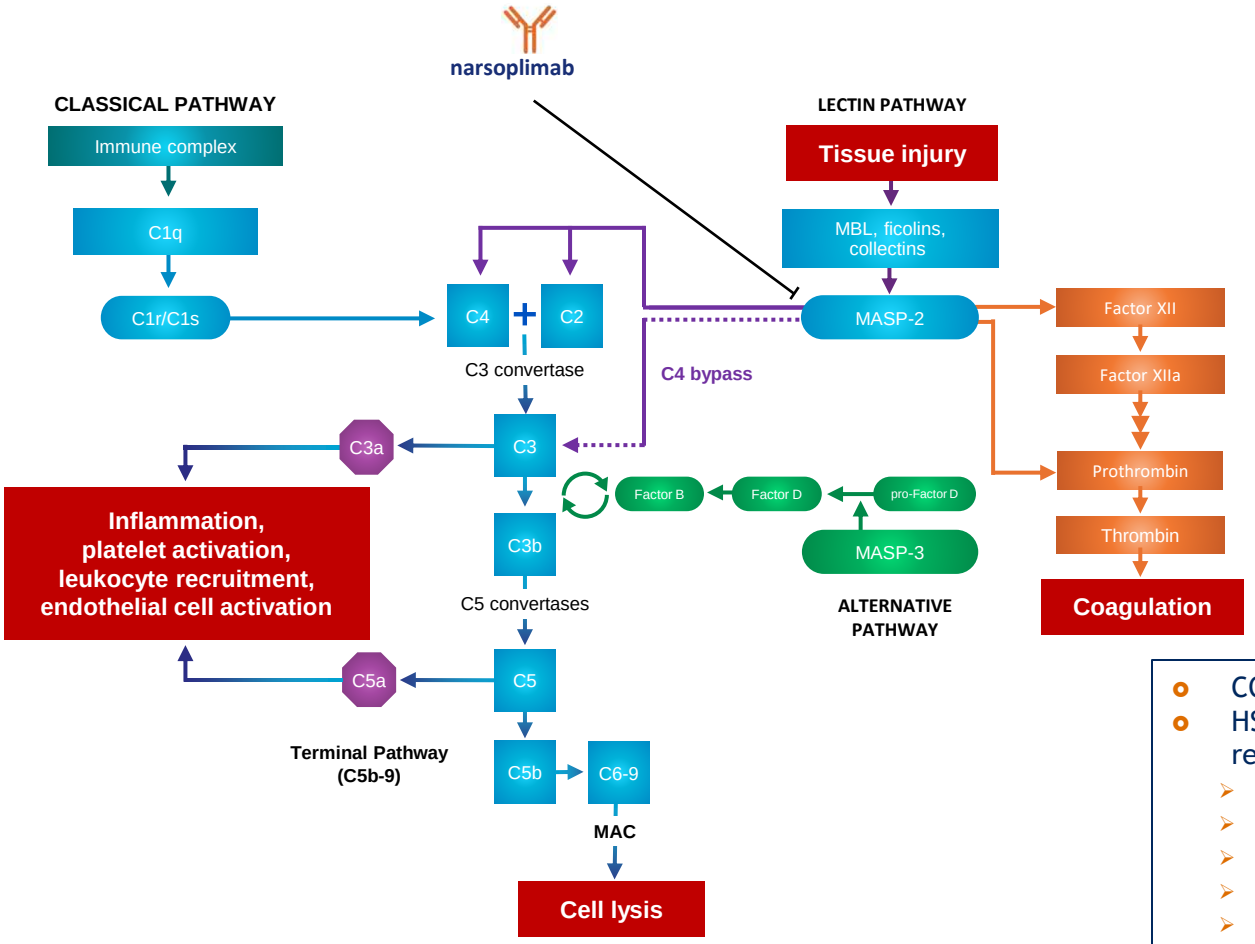
Narsoplimab – MASP-2 Inhibitor



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

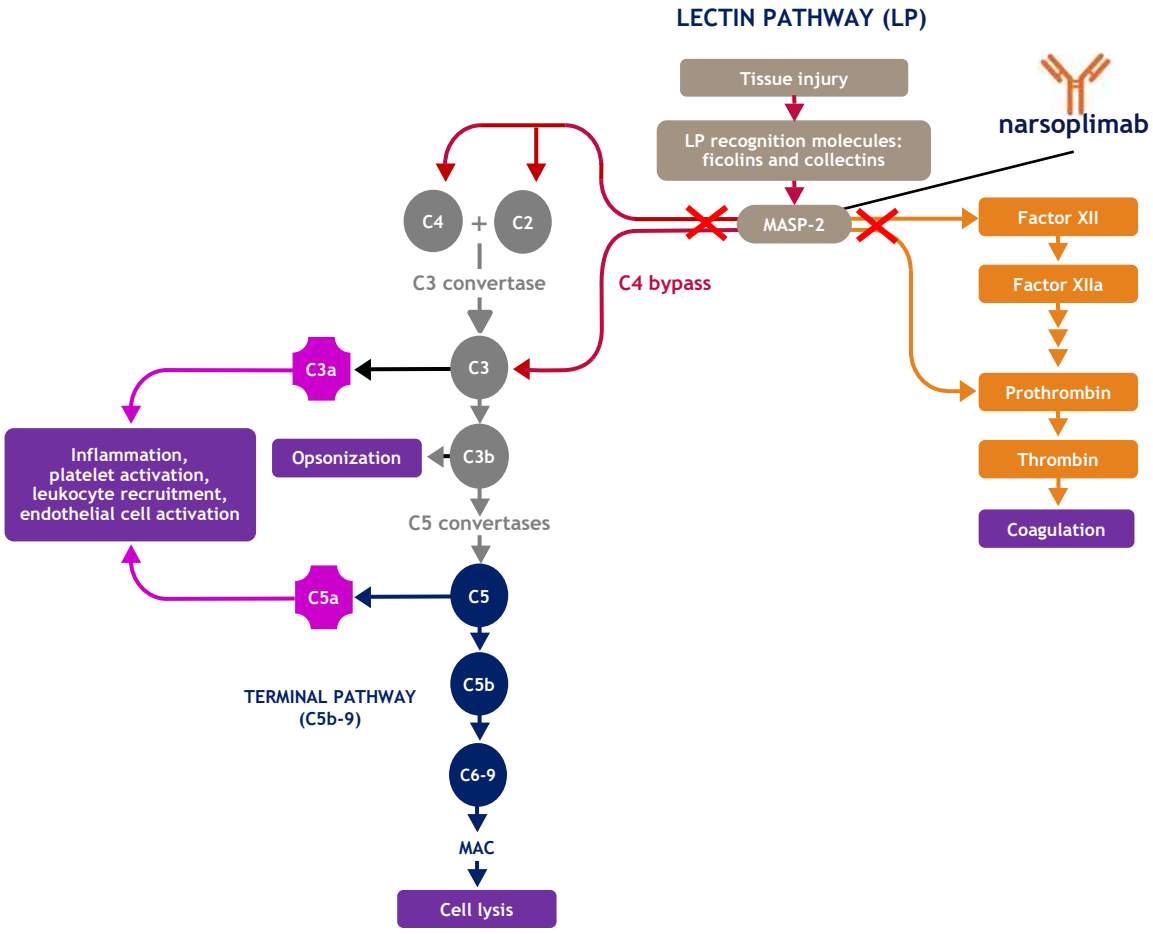


By blocking MASP-2, narsoplimab inhibits activation of the lectin pathway

Lectin Pathway Disorders

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

Narsoplimab Targets MASP-2 and the Lectin Pathway of Complement



Narsoplimab

- 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

Krarup A et al. 2007. PLoS ONE 2)7): e623; Gulla KC et al. Immunology 2009; 129, 482-495; Demopoulos G et al. W02019246367 (US20200140570A1). World International Property Organization. 26 Dec 2019; Kozarcanin H et al. Journal of Thrombosis and Haemostasis 2016. 14: 531-545.

Narsoplimab in Hematopoietic Stem Cell Transplant-Associated Thrombotic Microangiopathy

HSCT-TMA: A Serious and Potentially Fatal Complication of HSCT Caused by Endothelial Injury

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

No approved therapies for HSCT-TMA

incidence
of TMA in allogeneic HSCT

of patients with HSCT-TMA display at least one **high-risk** feature

of severe cases of HSCT-TMA can be **fatal**

Narsoplimab In HSCT-TMA: Pivotal Study

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

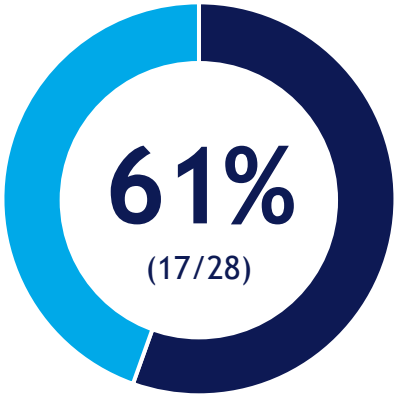
Efficacy Measures

- **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

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

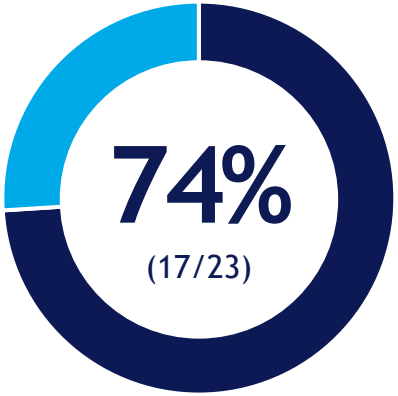
Complete Response Rates (%)

All treated patients (N=28)
(95% CI)



(40.6% to 78.5%)
p<0.0001*

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



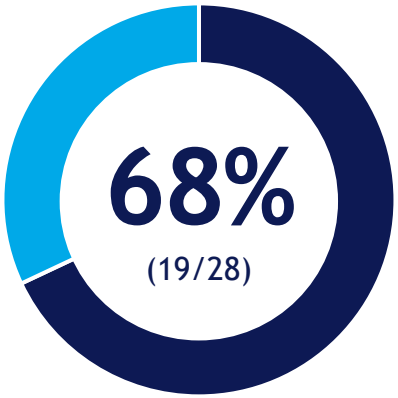
(51.6% to 89.8%)
p<0.0001*

- 15% is the FDA-agreed efficacy threshold for the primary endpoint (i.e., the complete response rate) in the clinical trial

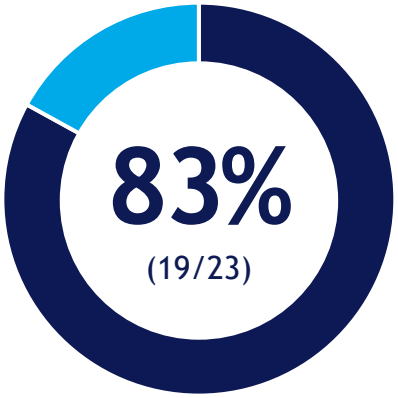
* Exact two-sided p-value for testing response rate equal to 15%

100-Day Survival Following HSCT-TMA Diagnosis

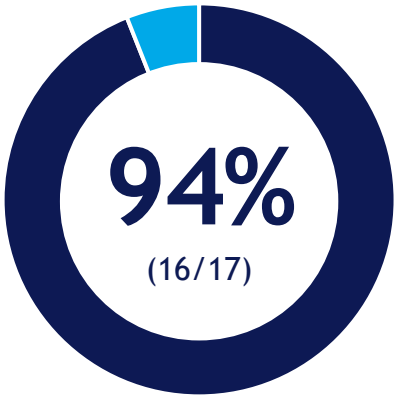
All treated patients (N=28)



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



Complete responders (n=17)



Patient Survival with Narsoplimab

Kaplan-Meier Plot of Overall Survival for HSCT-TMA

Median survival for the full analysis population was 274 days

(95% CI) (103, NE)

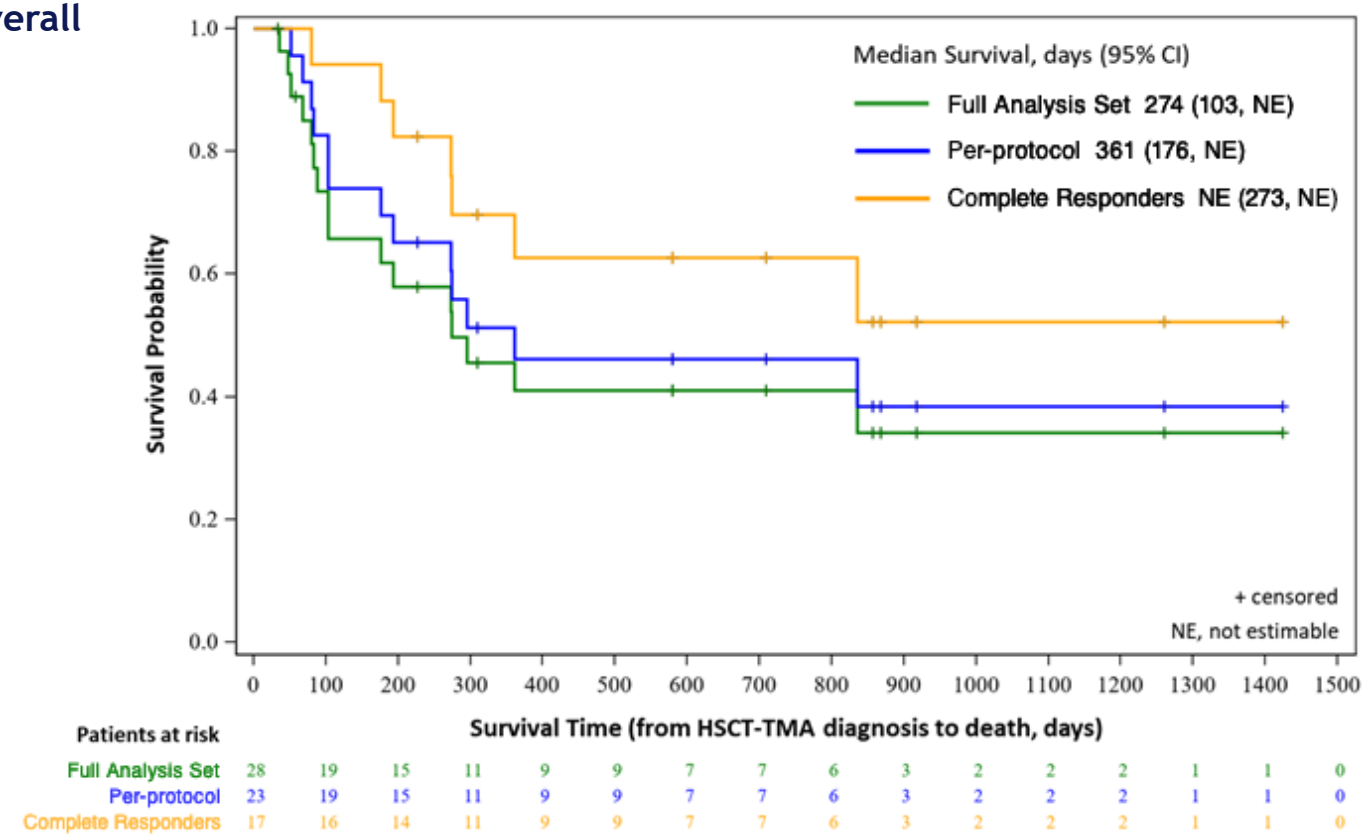
Median survival for the per-protocol population was 361 days

(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.



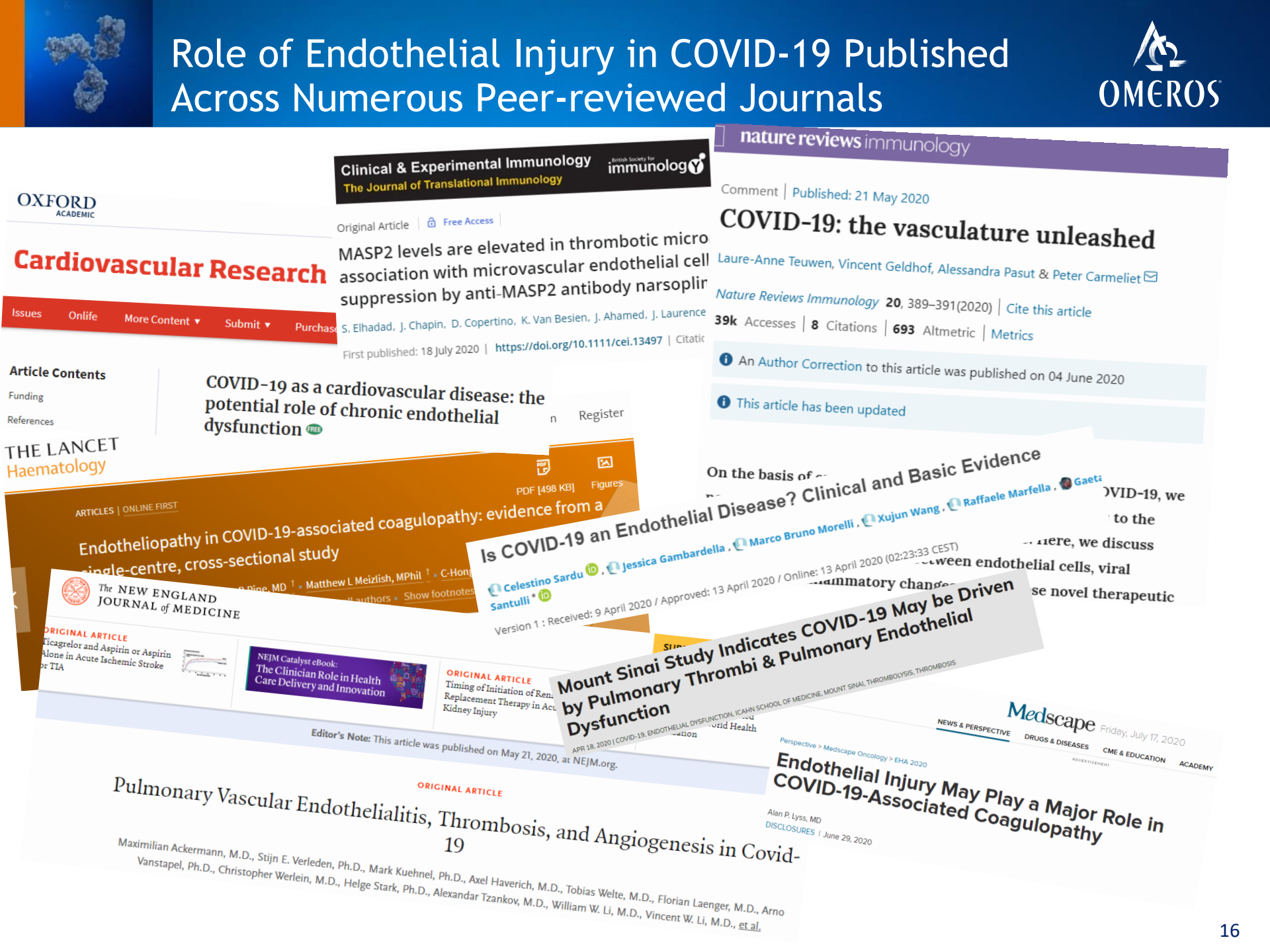
Safety and Tolerability: Most Common Adverse Events in >15% of Patients

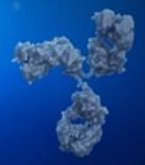
- Narsoplimab was well tolerated in this very sick population with multiple comorbidities
- The most commonly reported adverse events were nausea, vomiting, diarrhea, hypokalemia, neutropenia and fever
- The observed adverse events are comparable to those typically seen in the post-transplant population
- 6 patients died during the trial due to causes common in HSCT

Preferred Term, n (%)	(N = 28)
Any Event	27 (96.4)
Pyrexia	10 (35.7)
Diarrhea	9 (32.1)
Vomiting	9 (32.1)
Nausea	7 (25.0)
Neutropenia	7 (25.0)
Fatigue	6 (21.4)
Hypokalemia	6 (21.4)
Back pain	5 (17.9)

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

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- 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

Comparator	COVID-19	HSCT-TMA
Lectin-Pathway Activation from Endothelial Damage	✓	✓
Cause of Endothelial Injury	Viral	Conditioning regimen, Immunosuppressants, GVHD, infection
MASP-2 Activation	✓	✓
Multi-Organ TMA	✓	✓

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

Data from Cohort 1 of the COVID-19 Study in Italy[1]

OMEROS

Demographics and Treatment Summary

Demographic	Median (range) or n (%)
Age	57 years (47-63)
Male sex	5 (83%)
Weight	86 Kg (82-100 Kg)
Comorbidities	Diabetes (n=1); Hypertension (n=1); Dyslipidemia (n=2); Obese/Overweight (n=6)

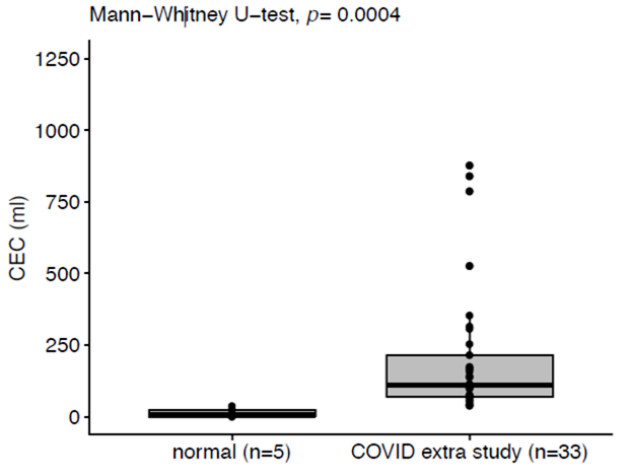
Treatment Summary	n (%) or Median (range)
Timing of narsoplimab treatment from start of CPAP oxygen support	
Within 24 hours	4 (67%)
Within 48 hours	2 (33%)
Time from hospital admission to treatment	2 days (1-4)
Duration of follow-up (to date) after first dose	27 days (16-90)

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%

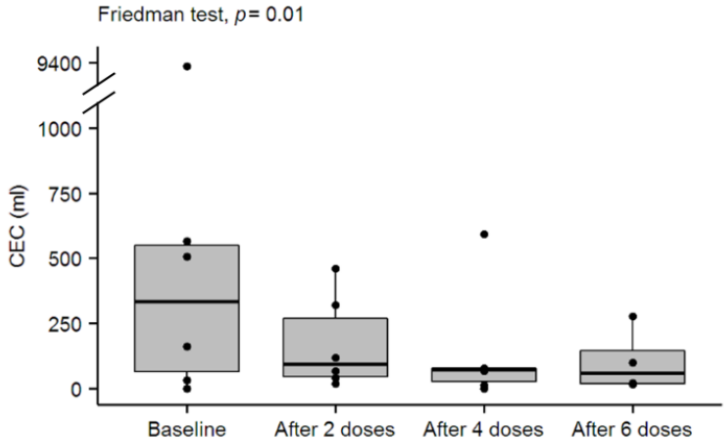
[1]Rambaldi, A. et al. Endothelial injury and thrombotic microangiopathy in COVID-19: treatment with the lectin-pathway inhibitor narsoplimab. *Immunobiology* https://doi.org/10.1016/j.imbio.2020.152001 (2020).

Data from Cohort 1 of the COVID-19 Study in Italy

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

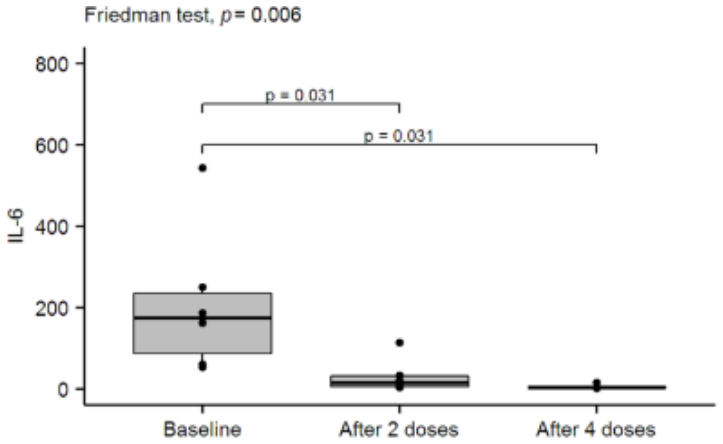


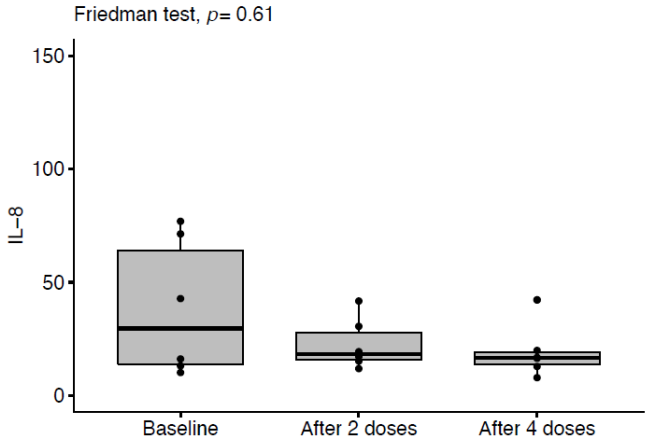
5 normal (uninfected) and 33 infected patients without Narsoplimab



6 infected patients treated with Narsoplimab

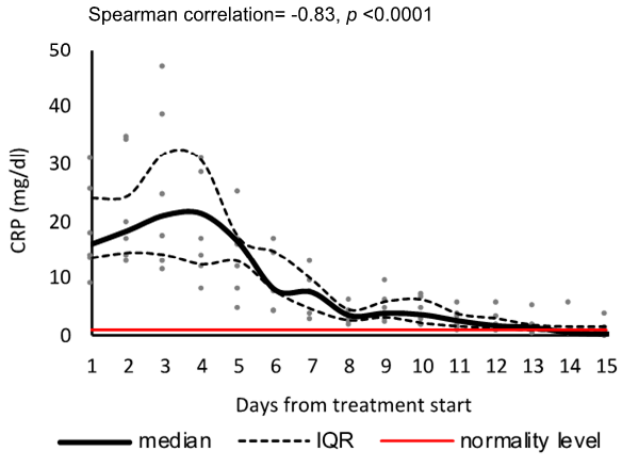
IL-6 / IL-8 Levels Improved in all 6 Patients Treated with Narsoplimab



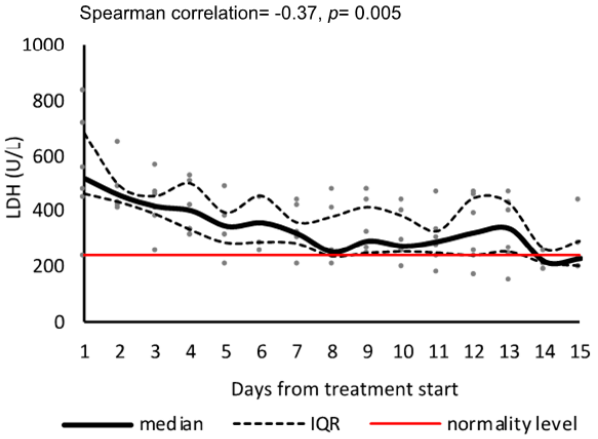


Data from Cohort 1 of the COVID-19 Study in Italy

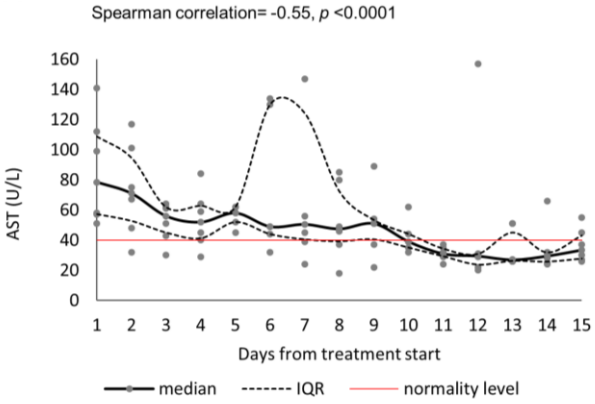
C-Reactive Protein
Improved in all 6 Patients



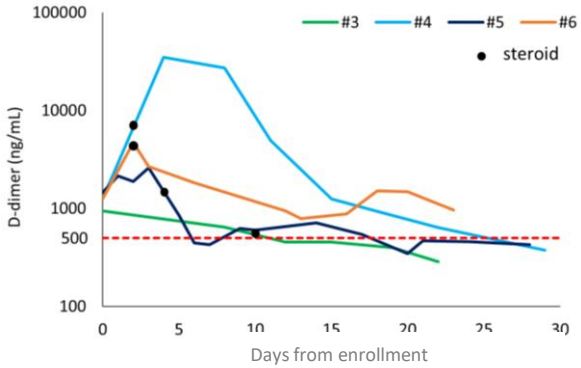
Lactate Dehydrogenase
Improved in all 6 Patients



Aspartate Aminotransferase (AST)
Improved in all 6 Patients



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

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

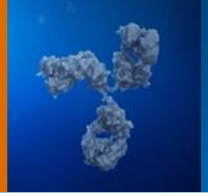
Clinical status at last evaluation of all 6 patients – no evidence of COVID sequelae

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

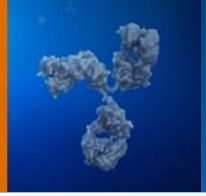
- Critically ill COVID-19 and HSCT-TMA patients share the same pathophysiology – both are endothelial injury syndromes
- Narsoplimab has been used to treat ~70 seriously ill COVID-19 and HSCT-TMA patients with striking results
- All COVID-19 patients treated with narsoplimab had ARDS requiring mechanical 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



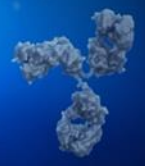
Narsoplimab CMC Status

- 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

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- 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

CMC Regulatory Issues for Consideration

- 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