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# Narsoplimab for Treatment of COVID-19, HSCT-TMA and Other Endothelial Injury Syndromes

November 2020

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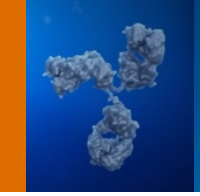

# Narsoplimab and Regulatory Status

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- Narsoplimab is a fully human IgG4 antibody against MASP-2, the effector enzyme of the lectin pathway of complement
- Completed pivotal clinical program in hematopoietic stem cell transplant-associated-TMA (HSCT-TMA)
- Completing rolling BLA for HSCT-TMA – will be submitted soon
- Enrolling 2 additional Phase 3 clinical programs – IgA nephropathy (IgAN) and atypical hemolytic uremic syndrome (aHUS)
- ~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
- Broad therapeutic areas for lectin pathway inhibition:
  - Endothelial injury syndromes
  - Proteinuric diseases
  - Ischemia-reperfusion injury
  - Dysregulation of inflammation (e.g., CNS)

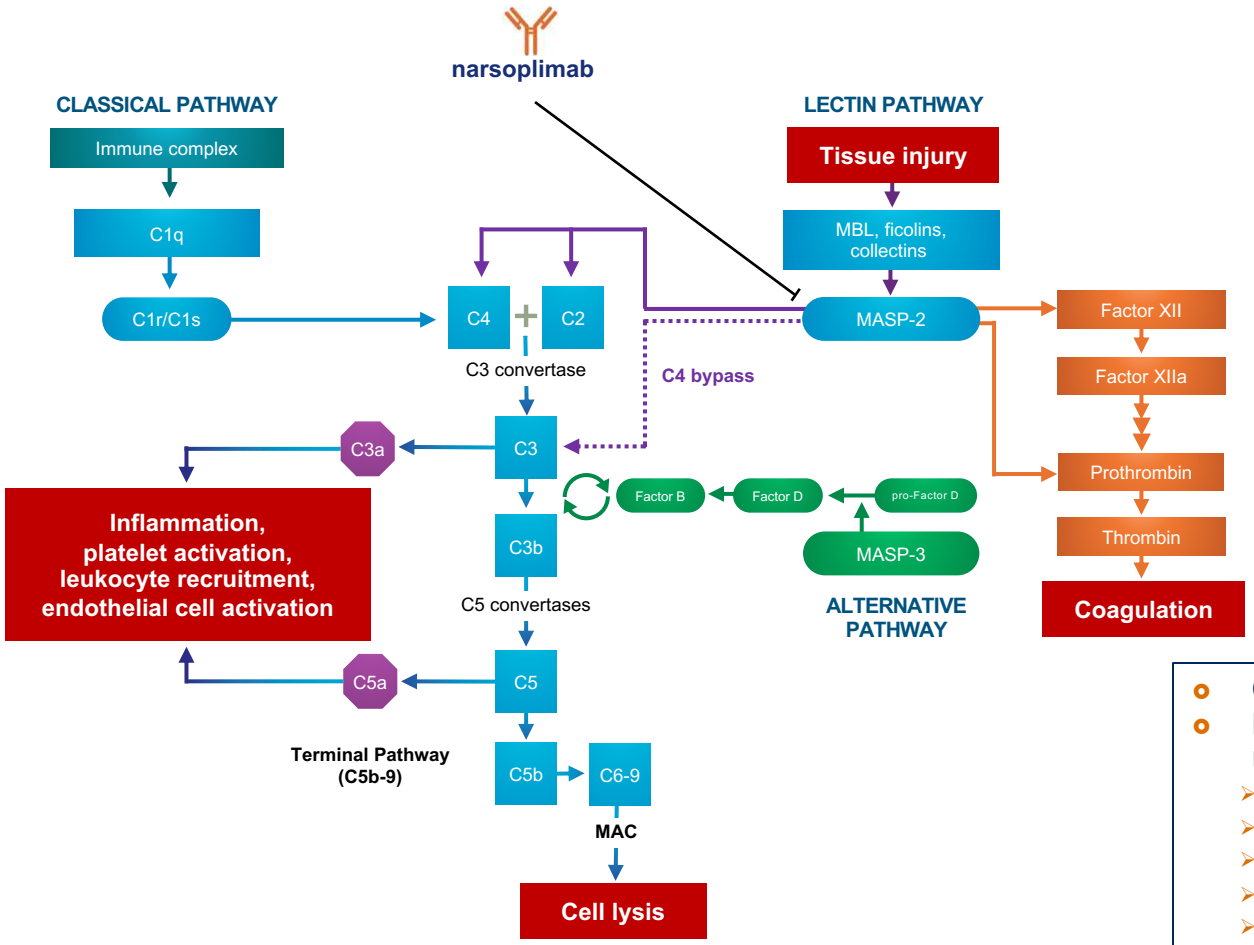
# Potential Advantages of Narsoplimab Over Other Complement Inhibitors

- Narsoplimab designed to leave classical and alternative pathways fully functional
  - Leaves the effector function of adaptive immune response intact
  - Maintains antigen-antibody complex-mediated lytic response and killing of virus-infected cells
  - No evidence of increased infection risk

- In addition to lectin pathway inhibition, narsoplimab observed to have anticoagulation effects, potentially beneficial in COVID-19 patients
  - Inhibits MASP-2-mediated cleavage of prothrombin to thrombin and activation of factor XII to XIIa, blocking thrombus formation
  - No prolongation of PT, aPTT or bleeding time
  - Inhibits MASP-2 activation of kallikrein

***Benefit:risk ratio heavily weighted toward benefit***

# Narsoplimab is a Potential Therapeutic for a Broad Range of Disorders, Including HSCT-TMA and COVID-19




## 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

# Endothelial Injury Plays a Major Role in Pathogenesis of a Wide Range of Diseases

**Endothelial injury plays a role** in the pathogenesis of:

| | | |
|---|---|---|
| Stroke | Viral infections (e.g. COVID-19) | Chronic kidney disease |
| Peripheral vascular disease | Stem cell transplant-related complications (e.g., TMA, aGVHD, VOD, DAH, IPS, CLS) | Venous thrombosis |
| Cancer | Heart disease | Diabetes |

Injury to endothelial cells occurs in many ways: physically, chemically, and immunologically

Damage to the vascular endothelium results in a procoagulant state and complement pathway activation

- Lectin pathway is a pattern-recognition system
- Lectin pathway is activated by carbohydrate patterns on microbes and surfaces of damaged cells

# Role of Endothelial Injury in COVID-19 Published Across Numerous Peer-reviewed Journals

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Article Contents

Funding

References

COVID-19 as a cardiovascular disease: the potential role of chronic endothelial dysfunction

Clinical & Experimental Immunology

The Journal of Translational Immunology

British Society for immunology

Original Article | Free Access

MASP2 levels are elevated in thrombotic micro

association with microvascular endothelial cell

suppression by anti-MASP2 antibody narsoplir

S. Elhadad, J. Chapin, D. Copertino, K. Van Besien, J. Ahamed, J. Laurence

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Comment | Published: 21 May 2020

COVID-19: the vasculature unleashed

Laure-Anne Teuwen, Vincent Geldhof, Alessandra Pasut & Peter Carmeliet

Nature Reviews Immunology 20, 389–391(2020) | Cite this article

39k Accesses | 8 Citations | 693 Altmetric | Metrics

An Author Correction to this article was published on 04 June 2020

This article has been updated

THE LANCET Haematology

ARTICLES | ONLINE FIRST

Endotheliopathy in COVID-19-associated coagulopathy: evidence from a

PDF [498 KB] Figures

Is COVID-19 an Endothelial Disease? Clinical and Basic Evidence

Celestino Sardu, Jessica Gambardella, Marco Bruno Morelli, Xujun Wang, Raffaele Marfella, Gaetz

Santulli

Version 1 : Received: 9 April 2020 / Approved: 13 April 2020 / Online: 13 April 2020 (02:23:33 CEST)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA

NEJM Catalyst eBook: The Clinician Role in Health Care Delivery and Innovation

ORIGINAL ARTICLE

Timing of Initiation of Ren Replacement Therapy in Acu Kidney Injury

Editor's Note: This article was published on May 21, 2020, at NEJM.org.

Mount Sinai Study Indicates COVID-19 May be Driven by Pulmonary Thrombi & Pulmonary Endothelial Dysfunction

APR 18, 2020 | COVID-19, ENDOTHELIAL DYSFUNCTION, ICAHN SCHOOL OF MEDICINE, MOUNT SINAI, THROMBOLYSIS, THROMBOSIS

Medscape Friday, July 17, 2020

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Perspective > Medscape Oncology > EHA 2020

Endothelial Injury May Play a Major Role in COVID-19-Associated Coagulopathy

Alan P. Lyss, MD

DISCLOSURES | June 29, 2020

ORIGINAL ARTICLE

Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19

Maximilian Ackermann, M.D., Stijn E. Verleden, Ph.D., Mark Kuehnel, Ph.D., Axel Haverich, M.D., Tobias Welte, M.D., Florian Laenger, M.D., Arno Vanstapel, Ph.D., Christopher Werlein, M.D., Helge Stark, Ph.D., Alexandar Tzankov, M.D., William W. Li, M.D., Vincent W. Li, M.D., et al.

# 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, binds the nucleocapsid protein of SARS-CoV-2 and activates the lectin pathway, leading to amplification of underlying cellular injury and inducing cytokine response (e.g., IL-6)
- 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** | ✓ | ✓ |

- Approximately 50 patients have been dosed with narsoplimab across the two EIS
- Marked improvement seen in narsoplimab-treated patients in these studies

# Compassionate Use of Narsoplimab for COVID-19 Patients in Bergamo, Italy

- 6 patient treated with narsoplimab, each included for presence of ARDS requiring mechanical ventilation (4 on CPAP, 2 intubated)
- Dosing IV twice weekly for 2 to 4 weeks
- All patients fully recovered, survived and were discharged
- 2 patients with massive bilateral pulmonary thromboses that resolved after narsoplimab treatment
- Temporal patterns of laboratory markers (CEC, IL-6, IL-8, CRP, LDH, AST and D-dimer) were consistent with the observed clinical improvement; in particular, CEC counts appear to be a reliable tool to evaluate endothelial damage and treatment response
- All patients received routine supportive care (prophylactic enoxaparin, azithromycin, hydroxychloroquine, darunavir/cobicistat) and, during the study, steroids (patient #1 did not receive steroids and patients 2 and 3 likely received no benefit from steroids given timing of initiation)
- Two control groups with similar entry criteria and baseline characteristics were selected for retrospective comparison showing substantial mortality rates of 32 percent and 53 percent
- Manuscript published in peer-reviewed *Immunobiology*

# Data from the COVID-19 Study in Italy

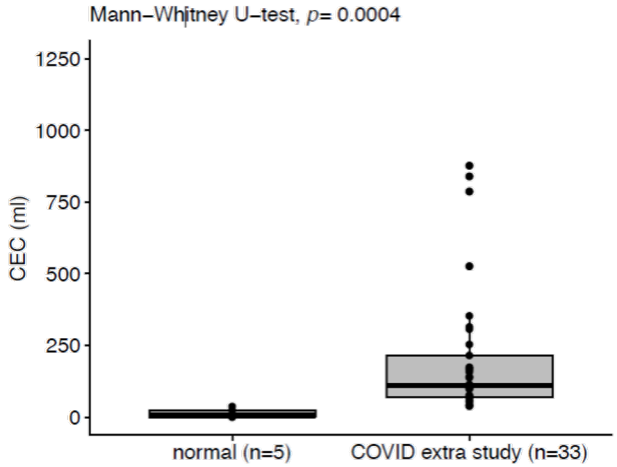
## Demographics and Treatment Summary

| 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) |

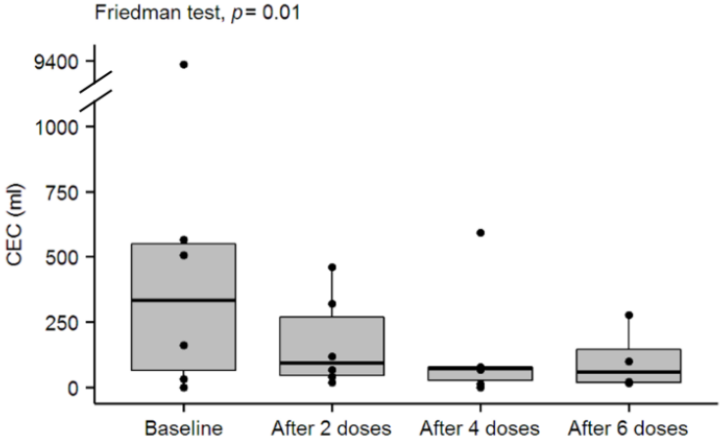
| Treatment Summary | n (%) or Median (range) |
|---|---|
| **Timing of narsoplimab treatment from start of CPAP oxygen support** | |
| ***Within 24 hours*** | 4 (67%) |
| ***Within 48 hours*** | 2 (33%) |
| **Time from hospital admission to treatment** | 2 days (1-4) |
| **Duration of follow-up (to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

# Data from the COVID-19 Study in Italy

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

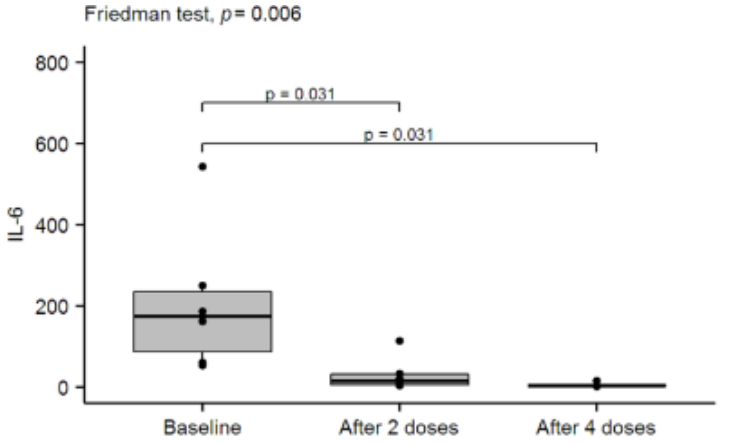


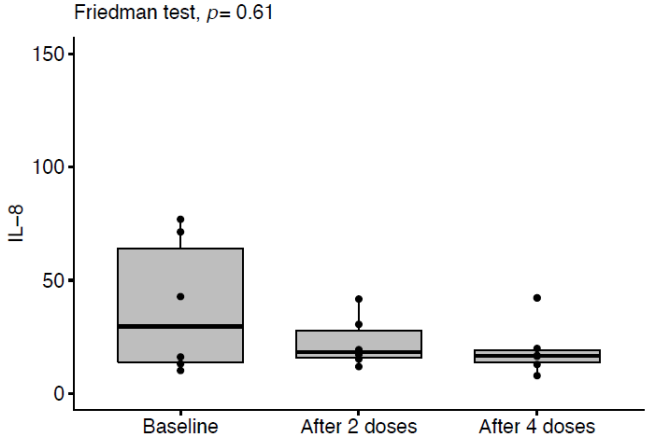

*5 normal (uninfected) and 33 infected patients without Narsoplimab*




*6 infected patients treated with Narsoplimab*

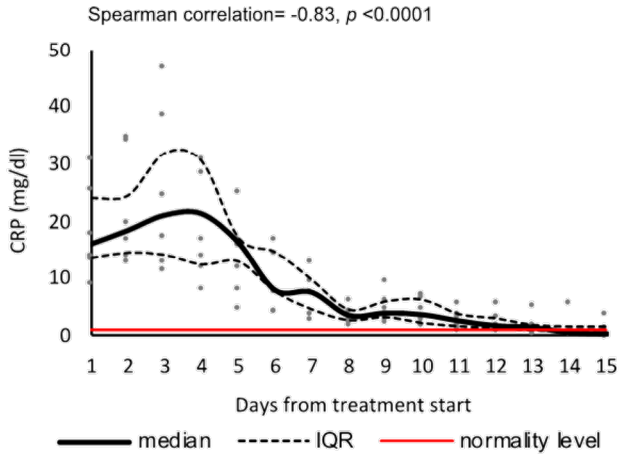
## IL-6 / IL-8 Levels Improved in 6 Patients Treated with Narsoplimab



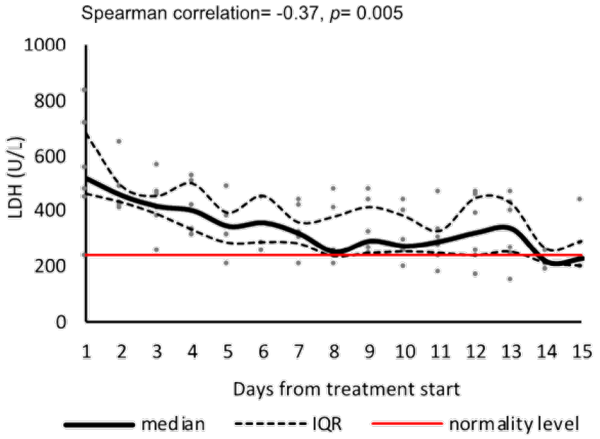



# Data from Narsoplimab-treated COVID-19 Patients

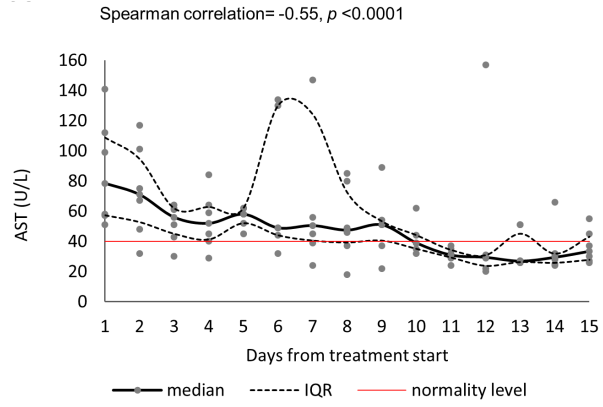
## C-Reactive Protein
## Improved in all 6 Patients



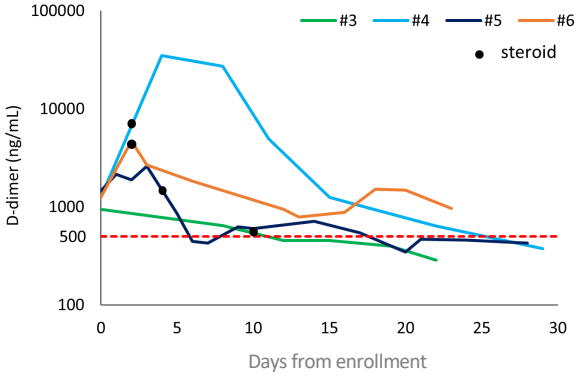

## Lactate Dehydrogenase
## Improved in all 6 Patients



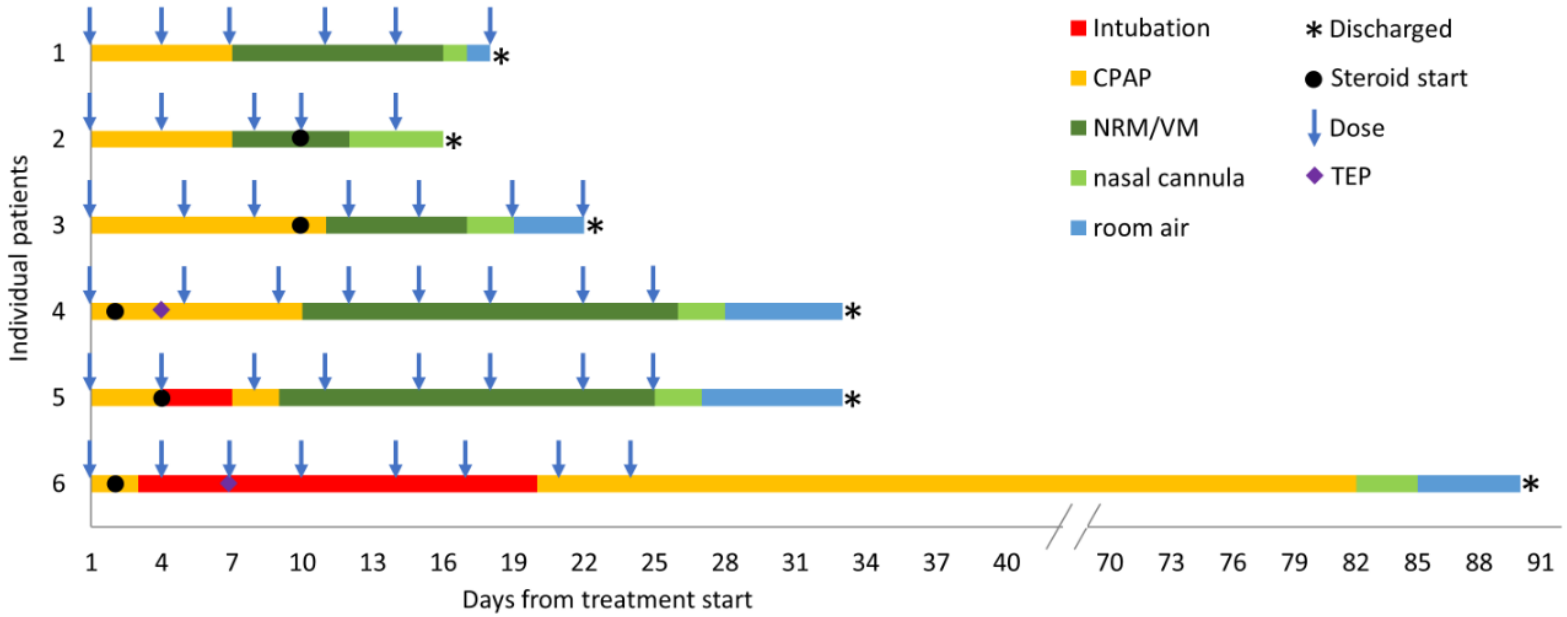

## Aspartate Aminotransferase (AST)
## Improved in all 6 Patients



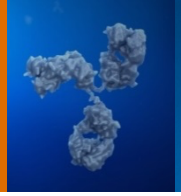

## D-Dimer
## Improved in all Assessed Patients



# Clinical Outcomes of COVID-19 Patients Treated with Narsoplimab




- The bar colors indicate the different oxygen support (CPAP = yellow; mechanical ventilation with intubation = red; non-rebreather oxygen mask/Venturi mask = green; low-flow oxygen by nasal cannula = light green; room air = blue)
- Narsoplimab doses are marked by blue arrows
- Black circle indicates the beginning of steroid treatment
- CPAP = continuous positive airway pressure; NRM = non-rebreather oxygen mask; VM = Venturi mask; TEP = pulmonary thromboembolism



# At 5-6 Month Follow-Up, All 6 Patients Are Without Clinical or Laboratory Evidence of Sequelae

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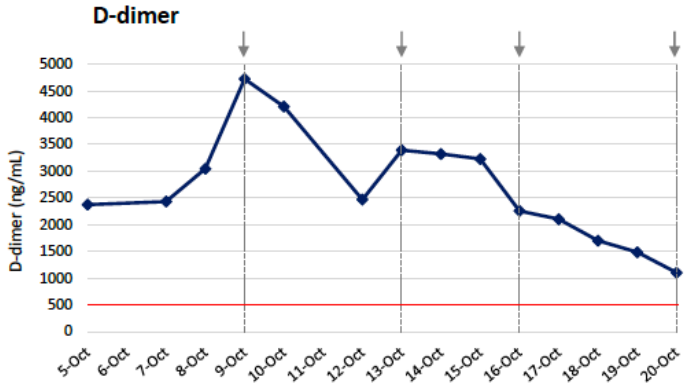
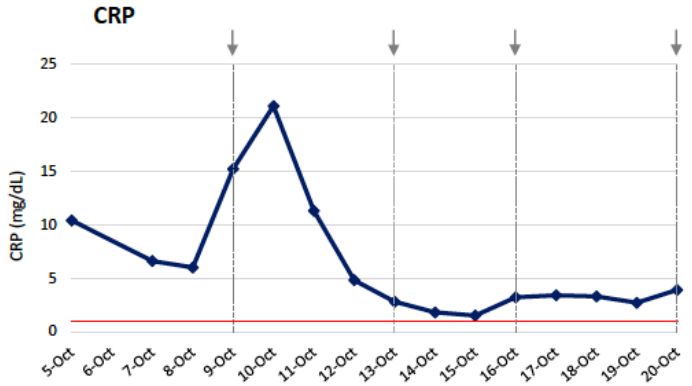
| Laboratory Findings | Baseline | Last Evaluation (5-6 Mos. Post-Discharge) |
|---|---|---|
| White cell count - per $mm^3$, median (range) | 8335 (6420-10,120) | 7320 (3200-8770) |
| > 10,000 per $mm^3$ - no. (%) | 2 (33) | 0 (0) |
| < 4000 per $mm^3$ - no. (%) | 0 (0) | 1 (17) |
| Lymphocyte count - 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) |

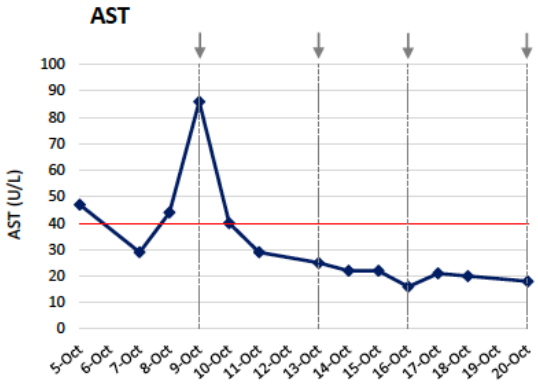
- Clinical status at last evaluation of all 6 patients – no evidence of post-COVID sequelae

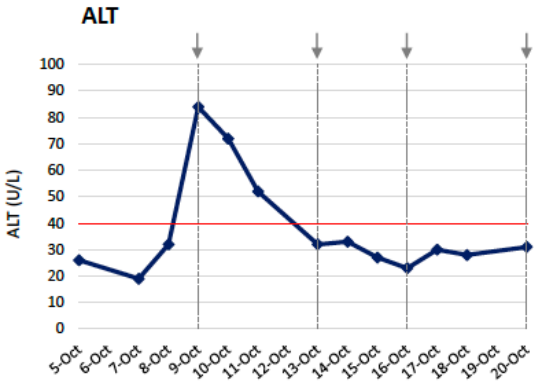
# Bergamo Patient #7 Undergoing Narsoplimab Treatment

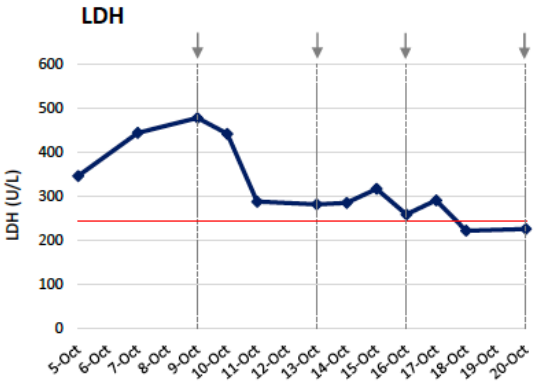
- 74-year-old man
- High-risk:  diabetic, obese, long history of smoking/COPD, prostate cancer
- Rapidly deteriorating pulmonary status: nasal cannulae → mask → CPAP → intubation
- Began treatment with narsoplimab following intubation; extubated around the 2nd dose




* Gray arrows denote dosing; Red lines denote normal value threshold

# Narsoplimab in HSCT-TMA

# HSCT-TMA – Serious and Potentially Fatal Complication of HSCT Caused by Endothelial Injury

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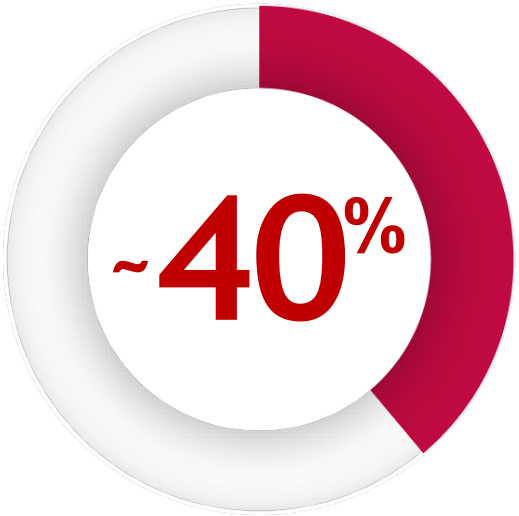
**25,000 – 30,000**
annual allogeneic HSCT in the US and EU

**No approved therapies in 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

| 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%) |

## Efficacy Measures

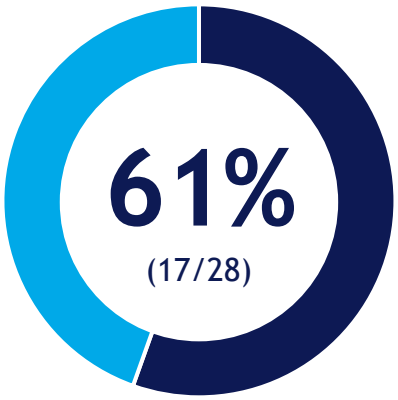
- **Primary Endpoint:** Response as assessed by clinically meaningful improvement in TMA laboratory markers and organ function
  - ***15% complete response rate is the FDA-agreed threshold for primary endpoint***
- **Secondary Endpoints:** 100-day survival and change from baseline in TMA lab measures

## Key Findings

- Most narsoplimab-treated patients achieved a complete response, exceeding the targeted threshold for the primary efficacy endpoint
- 100-day survival was similarly impressive across all groups (responders, per-protocol, and intent-to-treat)
- Narsoplimab was well tolerated in this very sick population with multiple comorbidities
- No safety signal observed: observed adverse events were comparable to those typically seen in post-transplant population
- 21% of patients died during the trial due to causes common in HSCT

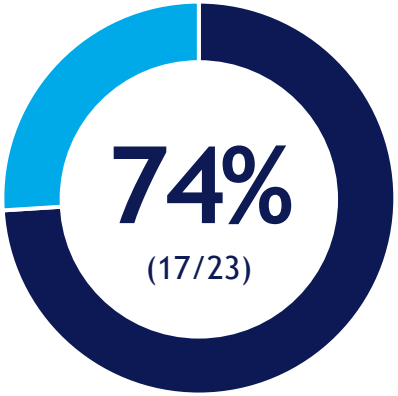
# Complete Response Rate (%)

**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)

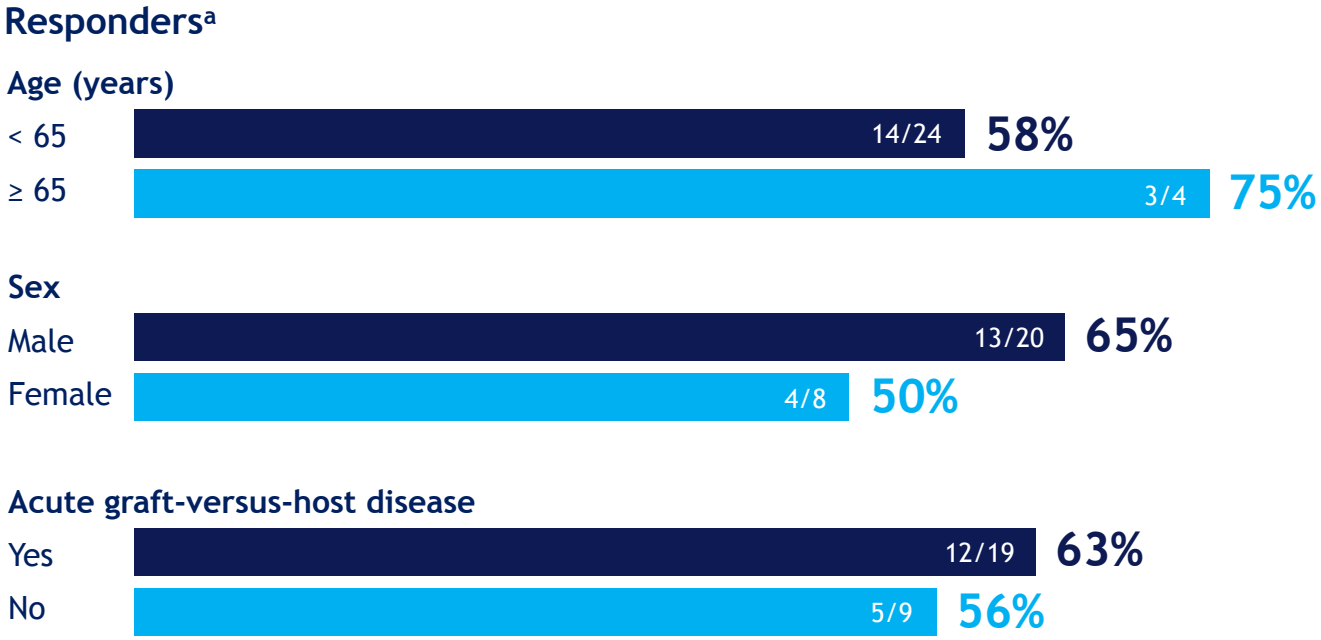



(51.6% to 89.8%)
p<0.0001*

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

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

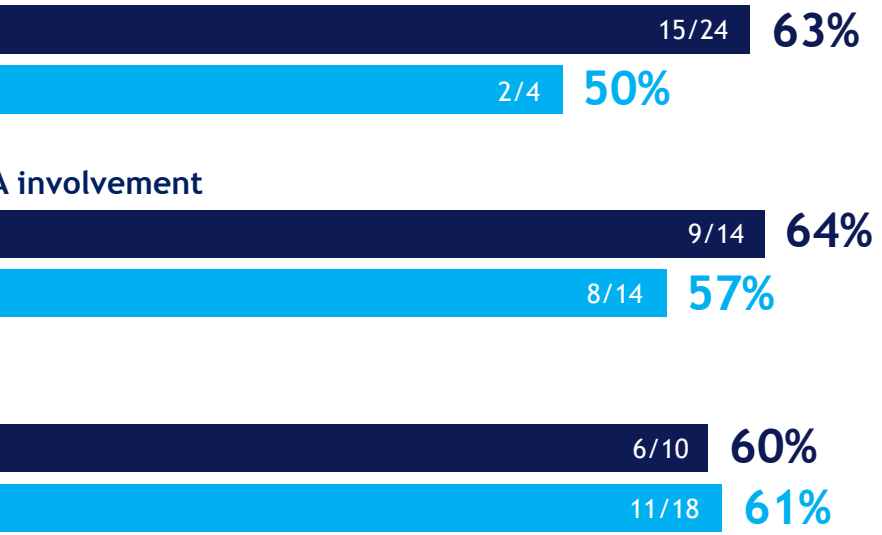
# Complete Response by Subgroup




[a] A responder is defined as achieving improvement in TMA markers and either improvement in organ functions or freedom from transfusion. Patients whose response cannot be determined are considered non-responders.

[b] m is the number of patients in the corresponding subgroup.

# Responders by Subgroup

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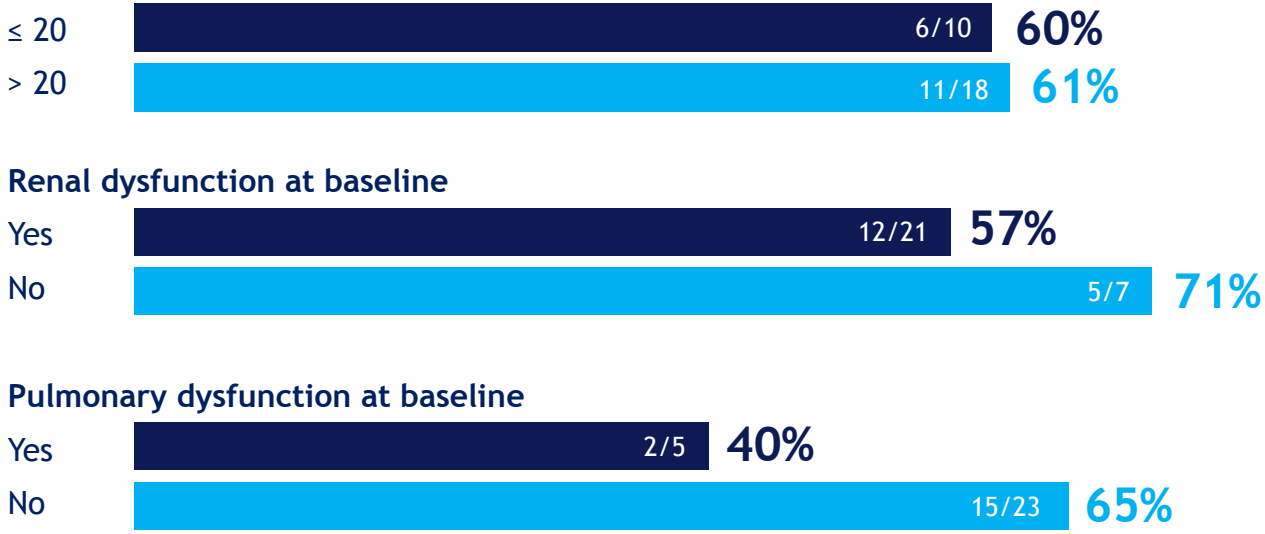


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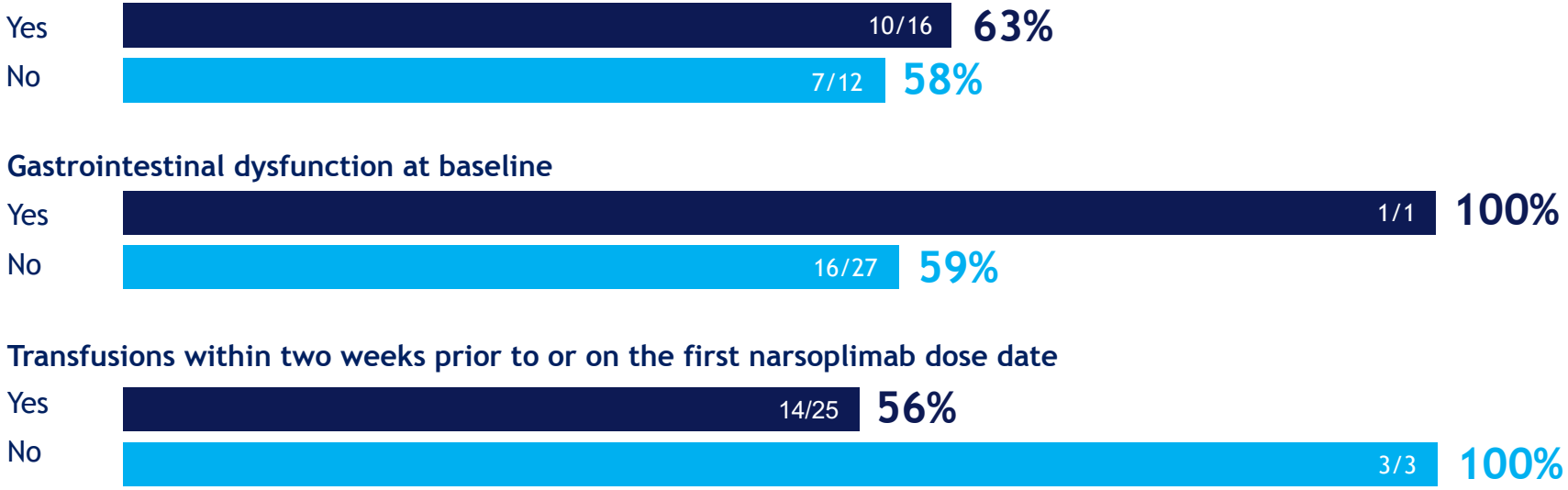


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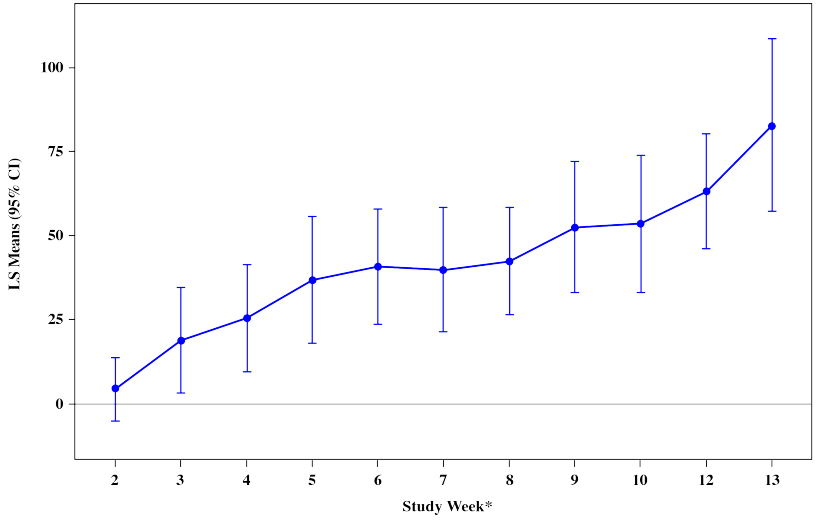
[b] m is the number of patients in the corresponding subgroup.

# Platelet Count and Hemoglobin Change from Baseline Over Time in Full Analysis Set

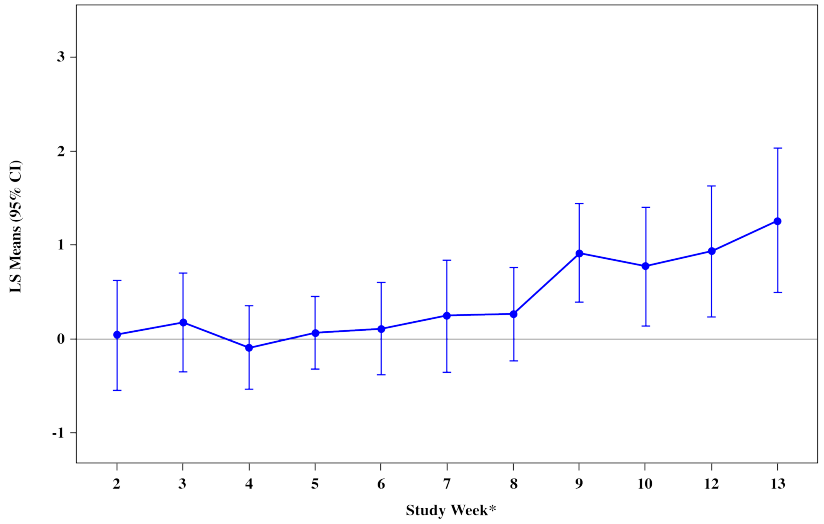
## Least Squares Means of Platelet Count (10^9/L) Change from Baseline for HSCT-TMA

Full Analysis Set Population




## Least Squares Means of Hemoglobin (g/dL) Change from Baseline for HSCT-TMA

Full Analysis Set Population



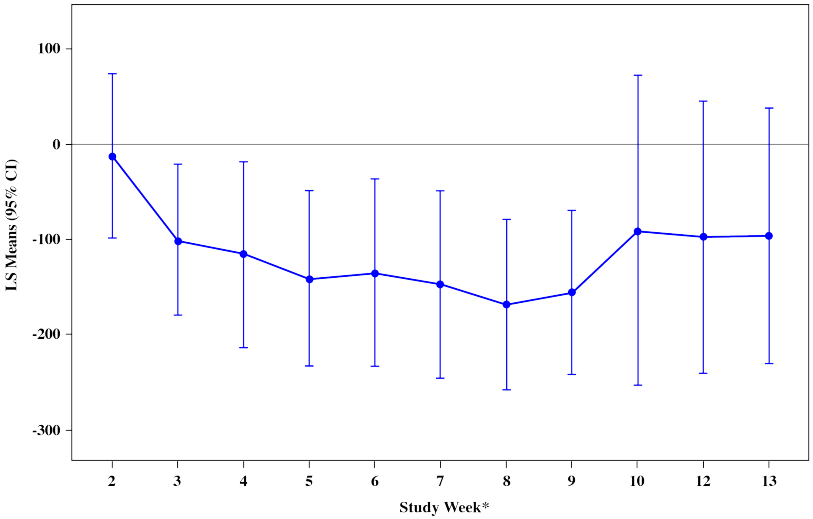

* No patient data were censored; all available data were included

** p-values from time-weighted average change-from-baseline using one-sample t test

# LDH and Haptoglobin
# Change from Baseline Over Time in Full Analysis Set

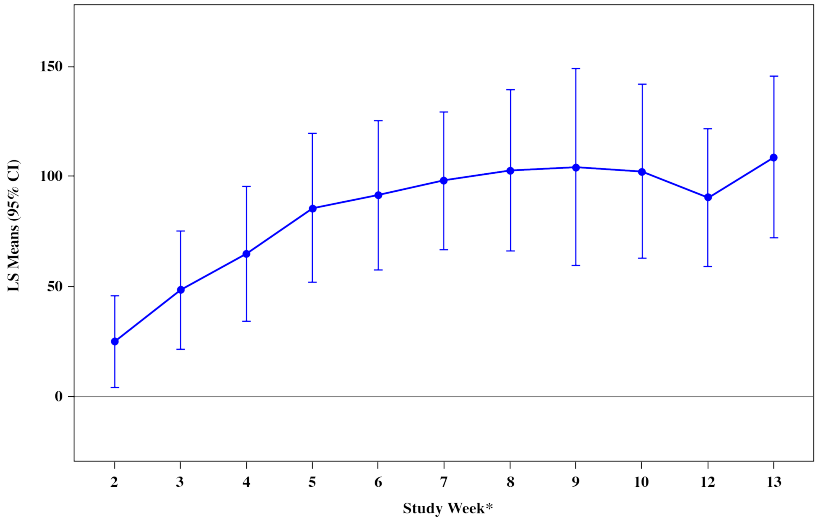
## Least Squares Means of LDH (U/L) Change from Baseline for HSCT-TMA

Full Analysis Set Population




## Least Squares Means of Haptoglobin (mg/dL) Change from Baseline for HSCT-TMA

Full Analysis Set Population

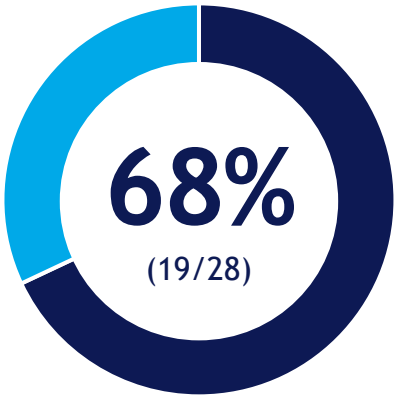



* No patient data were censored; all available data were included

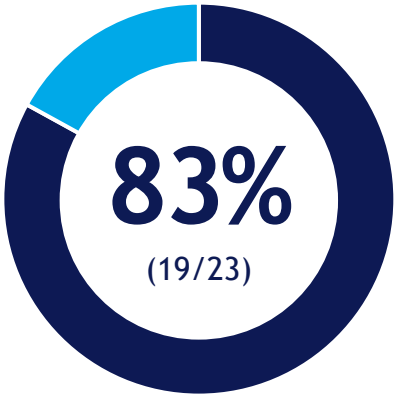
** p-values from time-weighted average change-from-baseline using one-sample t test

# 100-Day Survival Following HSCT-TMA Diagnosis

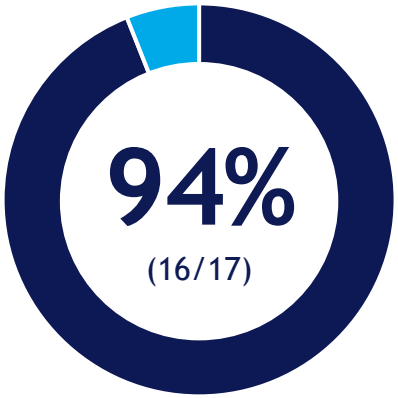
**All treated patients (N=28)**




**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)

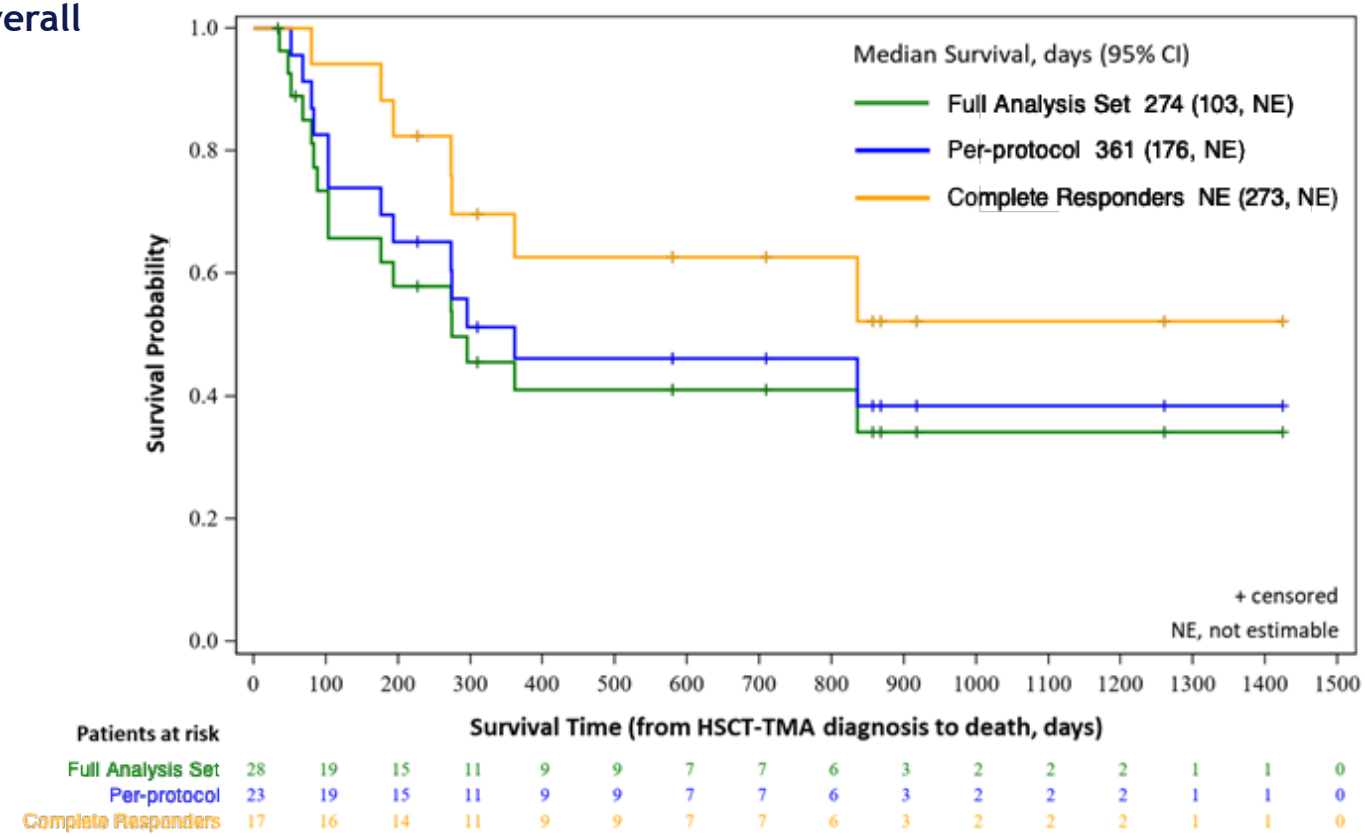
**Median survival for the per-protocol population was 361 days**

(95% CI) (176, NE)

**Median survival for the responder population was not estimable**

(95% CI) (273, NE)

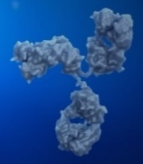
Median survival is estimated by Kaplan-Meier method. 95% confidence interval for median survival is calculated using complementary log-log transformation.



# 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
- 17.9% of 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) |



# HSCT-TMA Summary

OMEROS

- Narsoplimab is a fully human IgG4 antibody against MASP-2, the effector enzyme of the lectin pathway of complement
- Study patients were at high risk for poor outcomes
- Most narsoplimab-treated patients achieved a complete response with a significant improvement in laboratory markers and in clinical status
- 100-day survival was similarly impressive across all groups (responders, per-protocol, and full analysis)
- Robust response was seen in all patient subgroups defined by baseline characteristics, transplant characteristics, and transplant complications
- No safety signal was observed
- Data from the compassionate-use program are highly consistent with the clinical trial data
- Submitting rolling Biologics Licensing Application to FDA for HSCT-TMA
- European Marketing Authorization Application in preparation for same indication

# Next-Generation Therapeutics Transforming Patient Care Today