OMS906, a Novel Alternative Pathway MASP-3 Inhibitor, Improved Hematologic Parameters in Patients With PNH And Suboptimal Response to Ravulizumab Treatment: Phase 2 Dose-Finding Study Interim Results

Morag Griffin, MBChB, MRCP[1]; Richard J. Kelly, MBChB, PhD[1]; Mathilde Gavillet, MD, PhD[2]; Petra Muus, MD, PhD[1]; Britta Höchsmann, MD[3]; W. Jason Cummings, PhD[4]; Jane Humphreys, BSc[4]; Edward Philpot, MD[4]; John Efthimiou, BSc, MBBS, MD, FRCP[4]; William Pullman, BMedSc, MBBS, PhD, FRACP[4]; Hubert Schrezenmeier, MD[3]; Jens Panse, MD[5]

[1]Leeds Teaching Hospitals NHS Trust, Leeds, UK; [2]Service and Central Laboratory of Hematology, Department of Oncology, Lausanne University Hospital (CHUV), Lausanne, Switzerland; [3]Institute of Transfusion Medicine, University of Ulm, and Institute of Clinical Transfusion Medicine, German Red Cross Blood Transfusion Service and University Hospital Ulm, Ulm, Germany; [4]Omeros Corporation, Seattle, WA, USA; [5]Universitätsklinikum RWTH Aachen, Germany

Presented at the EHA2024 Hybrid Congress | June 13–16, 2024 | Madrid, Spain

Author Disclosures

- **MGr: Advisory board – Alexion, Amgen, Novartis, Omeros, Pfizer, Sobi; Speaker's bureau – Alexion, Pfizer, Sobi; Consultancy – Biocryst, Regeneron**
- **RJK:** Research funding – Novartis; Consultancy – Otsuka, Sobi; Advisory committee – Alexion, Jazz, Novartis, Roche, Sobi; Speakers' bureau – Alexion, Astellas, Novartis, Otsuka, Sobi
- **MGa:** Consultancy – Alexion, Appletree, Sobi, Vertex
- **PM:** Advisory board – Novartis, Roche; Travel support – Alexion, Sobi; Lecture fee – Sobi
- **WJC:** Employee – Omeros
- **JH, EP, JE, WP:** Clinical consultants – Omeros
- **HS:** Research funding – Alexion, AstraZeneca Rare Disease, Novartis, Sobi; Advisory board – Alexion, Amgen, AstraZeneca Rare Disease, Novartis, Omeros, Roche, Sanofi, Sobi; Speaker's bureau – AstraZeneca Rare Disease (all to the institution; University Hospital Ulm), Novartis
- **JP:** Advisory committee – Apellis Pharmaceuticals, Inc, Blueprint Medicines, BMS, MSD, Samsung Bioepis Co Ltd, Sobi, Sanofi; Speaker's bureau and Advisory committee – Alexion (AstraZeneca Rare Disease), Boehringer Ingelheim, Blueprint Medicines, Novartis, Pfizer, Sobi

Terminal Complement (C5) Inhibition Attenuates Intravascular Hemolysis but Induces Extravascular Hemolysis[1,2]

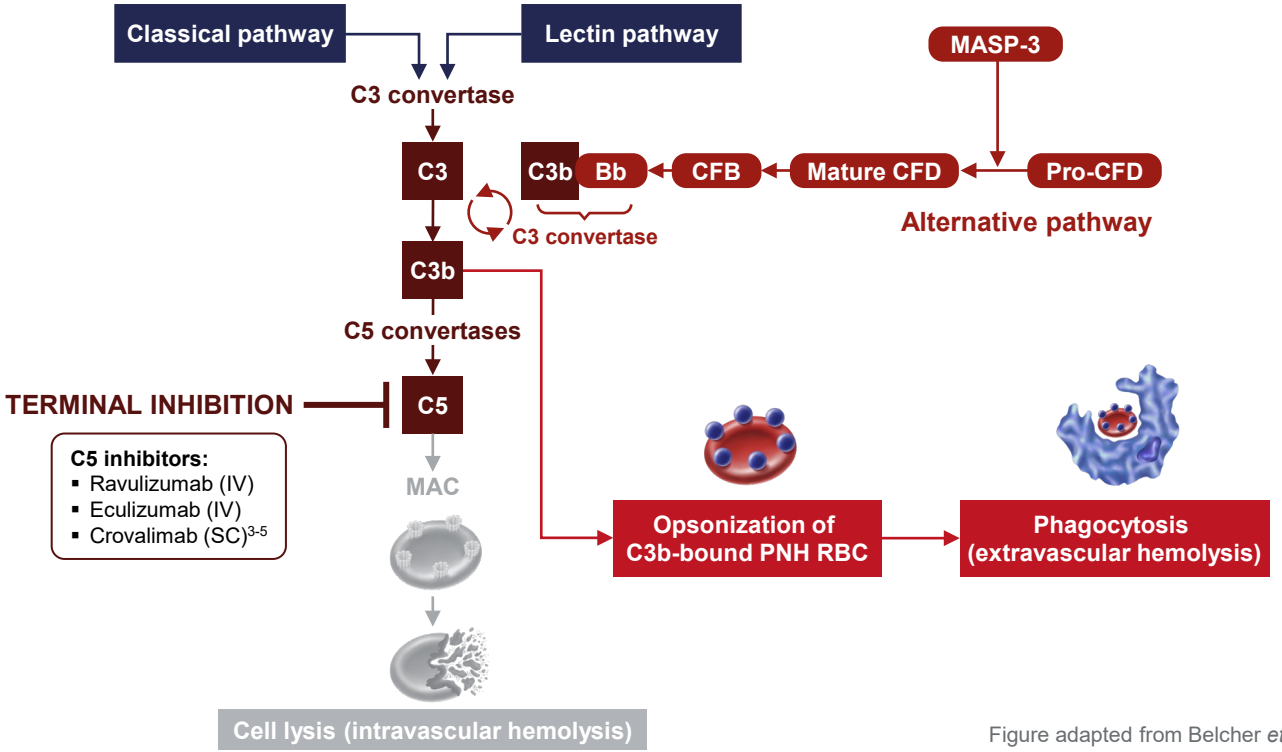
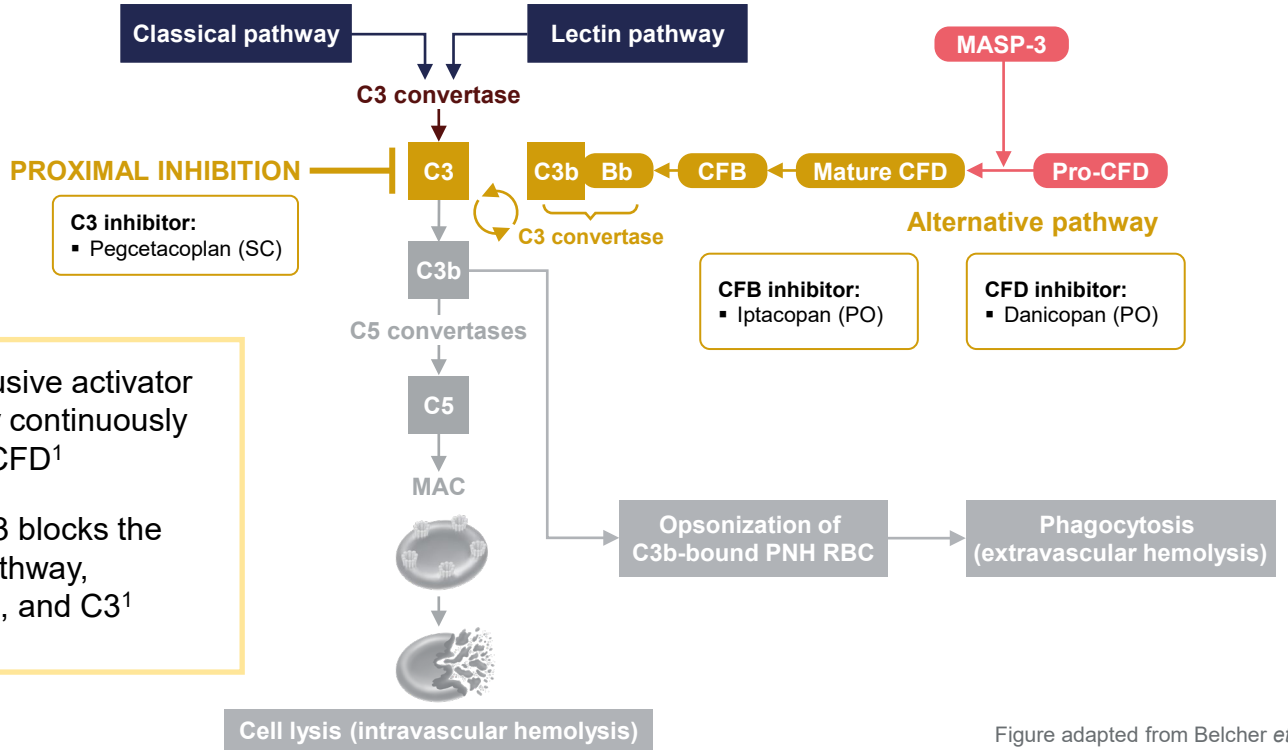


Figure adapted from Belcher *et al.* (2022)[6]

CFB, complement Factor B; CFD, complement Factor D; IV, intravenous; MAC, membrane attack complex; MASP-3, mannan-binding lectin-associated serine protease-3; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; SC, subcutaneous.

1. Notaro R *et al. N Engl J Med*. 2022;387:160–6. **2.** Risitano AM *et al. Immunol Rev*. 2023;313:262–78. **3.** Röth A *et al. HemaSphere* 2023;7(S3):S181. **4.** Scheinberg P *et al. HemaSphere* 2023;7(S3):S183. **5.** Liu H *et al. HemaSphere* 2023;7(S3):P785. **6.** Belcher JD *et al. Transl Res*. 2022;249:1–12.

MASP-3 is an Upstream Activator of the Alternative Pathway and a Novel Target for the Treatment of PNH[1,2]



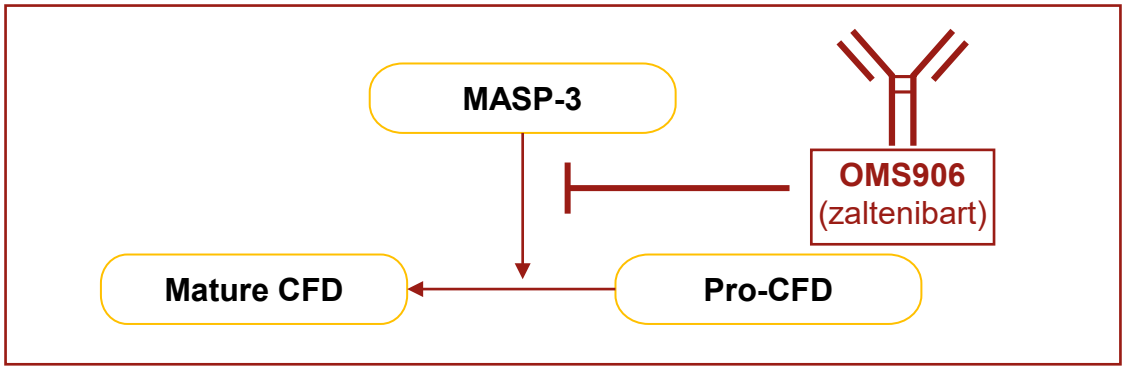
- MASP-3 is the exclusive activator of pro-CFD, thereby continuously generating mature CFD[1]
- Inhibition of MASP-3 blocks the entire alternative pathway, including CFD, CFB, and C3[1]

Figure adapted from Belcher *et al.* (2022)[3]

CFB, complement Factor B; CFD, complement Factor D; MAC, membrane attack complex; MASP-3, mannan-binding lectin-associated serine protease-3; PNH, paroxysmal nocturnal hemoglobinuria; PO, per os; RBC, red blood cell; SC, subcutaneous.

1. Sekine H *et al. Immunol Rev* 2023;313:15–24. **2.** Barratt J, Weitz I. *Front Immunol* 2021;12:712572. **3.** Belcher JD *et al. Transl Res.* 2022;249:1–12.

OMS906 (zaltenibart) is a Highly Selective Humanized IgG4 mAb That Binds to and Inhibits MASP-3[1,2]

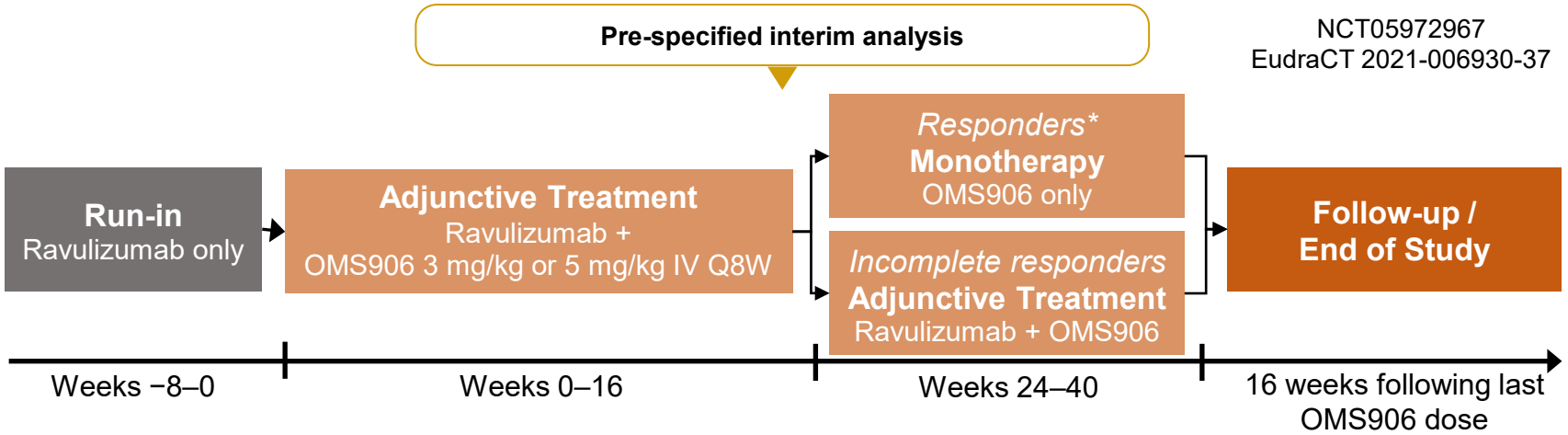


- OMS906 can be administered SC or IV[2]
- In a Phase 1 study in healthy subjects, OMS906 was well tolerated, with 5 mg/kg IV showing near complete inhibition of MASP-3 through Day 71[2]
- In a Phase 1b study in treatment-naïve patients with PNH, OMS906 5 mg/kg SC was well tolerated, normalized hemoglobin levels, and increased RBC clone size over 24 weeks[3]

CFD, complement Factor D; IgG, immunoglobulin G; IV, intravenous; mAb, monoclonal antibody; MASP-3, mannan-binding lectin-associated serine protease 3; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; SC, subcutaneous.

1. Cummings WJ *et al. Mol Immunol* 2022;150:145. **2.** Griffin M *et al. HemaSphere* 2023;7(S3):P787. **3.** Karnabeda O *et al. Blood.* 2023:142(S1):573.

Study Design for the Ongoing Open-Label Phase 2 Trial of OMS906 for Patients With PNH and Suboptimal Response to Ravulizumab



Key Inclusion Criteria:

- Adults with confirmed PNH diagnosis by flow cytometry (RBCs and/or granulocytes clone size >10%)
- Suboptimal response to ravulizumab (baseline Hgb <10.5 g/dL despite ≥2 doses [4 months] of ravulizumab)

Primary Endpoint:

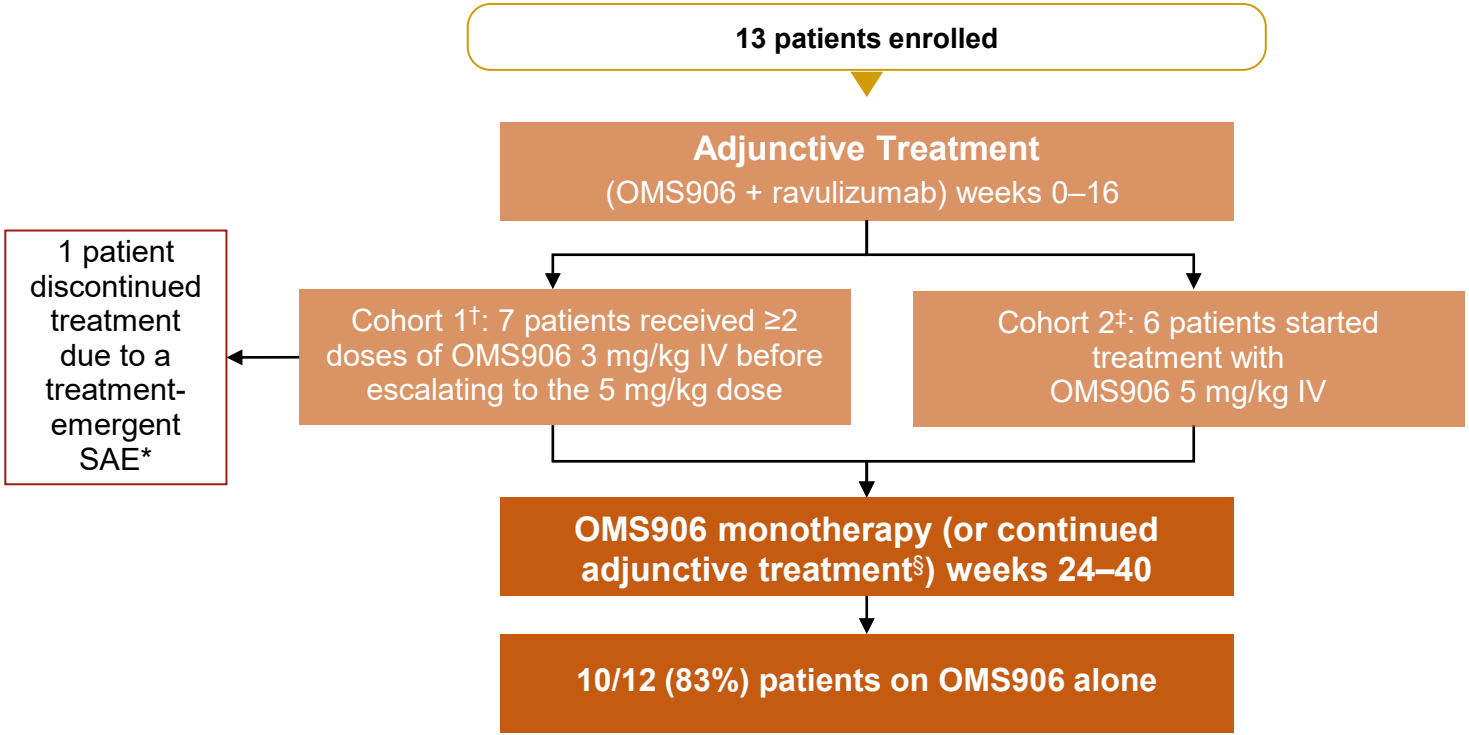
- Safety and tolerability

Key Secondary Endpoints:

- Preliminary efficacy by effect on anemia and hemolysis:
  - Change from baseline in Hgb level, LDH level, ARC, number of transfusions
- PK, PD, and anti-drug antibodies

*Response is defined as an increase in Hgb levels ≥2.0 g/dL at week 24.
ARC, absolute reticulocyte count; Hgb, hemoglobin; IV, intravenous; LDH, lactate dehydrogenase; PD, pharmacodynamic; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria; Q8W, every 8 weeks; RBC, red blood cell.

As of the Cut-Off Date, 13 Patients With PNH Received Treatment With Ravulizumab and OMS906



*Elevated ALT and bilirubin with prior elevated values. †Started at 3 mg/kg. ‡Started at 5 mg/kg. §Monotherapy stage: all patients on 5 mg/kg but could continue with adjunctive ravulizumab (n=2) based on Investigator discretion.

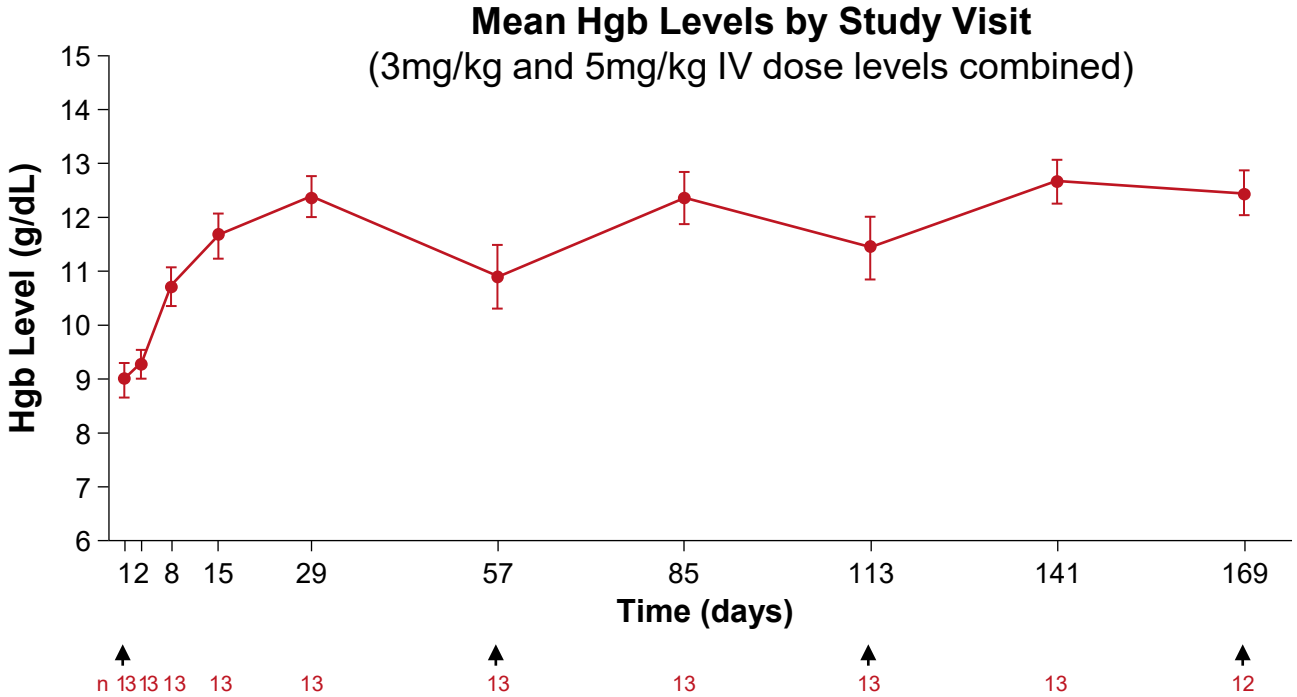
ALT, alanine aminotransferase; IV, intravenous; PNH, paroxysmal nocturnal hemoglobinuria; SAE, serious adverse event.

OMS906-PNH-001: Patient Demographics

Baseline demographics and clinical characteristics	OMS906 N=13	
Baseline demographics	**Mean (SD)**	**Median (range)**
Age, years	53.2 (18.3)	52 (23–80)
Weight, kg	76.3 (17.3)	78 (55.6–115.2)
Female, n (%)	7 (53.8)	
Caucasian, n (%)	10 (76.9)	
PNH disease characteristics	**Mean (SD)**	**Median (range)**
Time since PNH diagnosis, years	12.8 (10.3)	12 (2–37)
PNH granulocyte clone size (%)	88.4 (22.3)	99.3 (31.1–99.9)
Patients receiving RBC transfusions*, n (%)	6 (46.2)	
Laboratory markers at baseline†	**Mean (SD)**	**Median (range)**
Hgb, g/dL	8.98 (1.21)	9.1 (6.6–10.8)
LDH,† U/L	285.69 (85.41)	270 (170–468)
Absolute reticulocyte count (ARC), $\times 10^9$/L	227.7 (90)	204.9 (100–400)
Medical history, n (%)		
Aplastic anemia	6 (46.2)	

*At least one transfusion prior to starting OMS906 treatment. †Median ULN, 246 IU/L (Local labs, CH ULN=214, UK ULN=246, DE ULN=249).
Hgb, hemoglobin; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; SD, standard deviation; ULN, upper limit of normal.

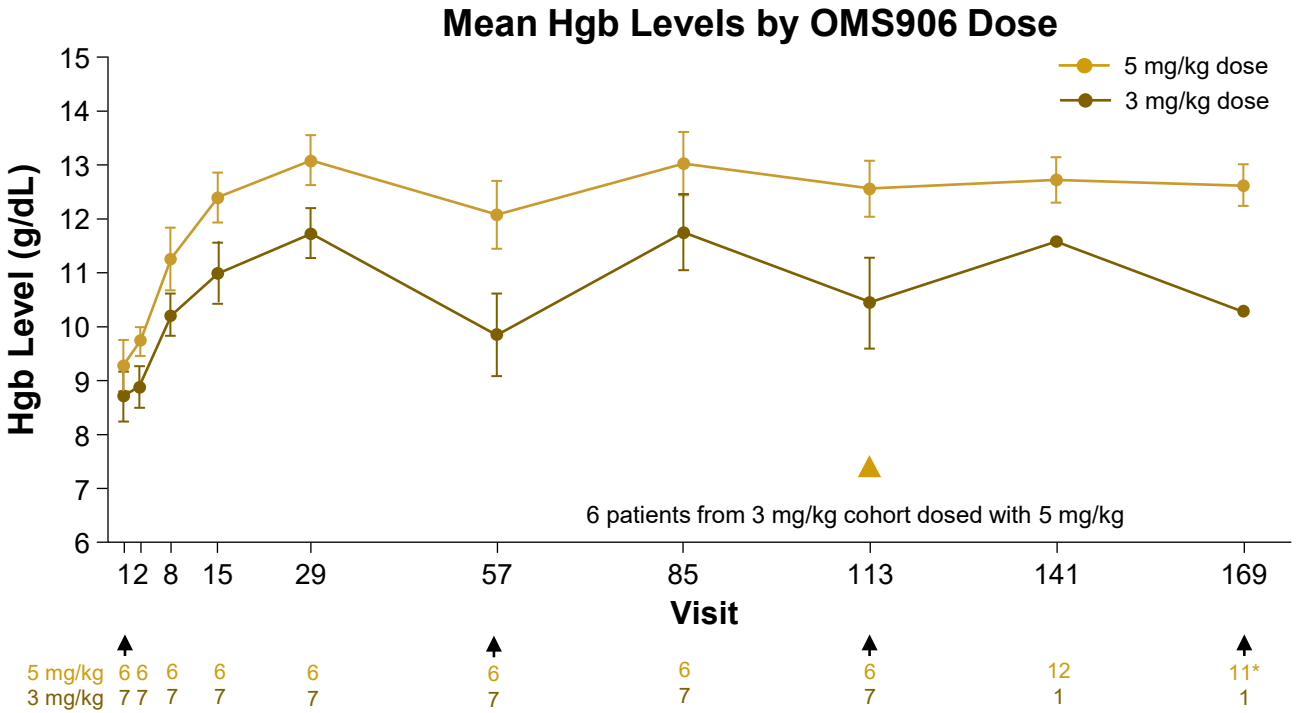
In Patients With Suboptimal Response to Ravulizumab, the Addition of OMS906 Treatment Rapidly Improved Hgb Levels



- At Day 29, mean Hgb increased by 3.39 g/dL (N=13; *P*<0.0001)
- At Day 169, mean Hgb increased by 3.27 g/dL (N=12; *P*<0.0001)

Response is defined as an increase in Hgb levels ≥2.0 g/dL. Arrows indicate OMS906 administration. Each timepoint depicts a study visit.
Hgb, hemoglobin.

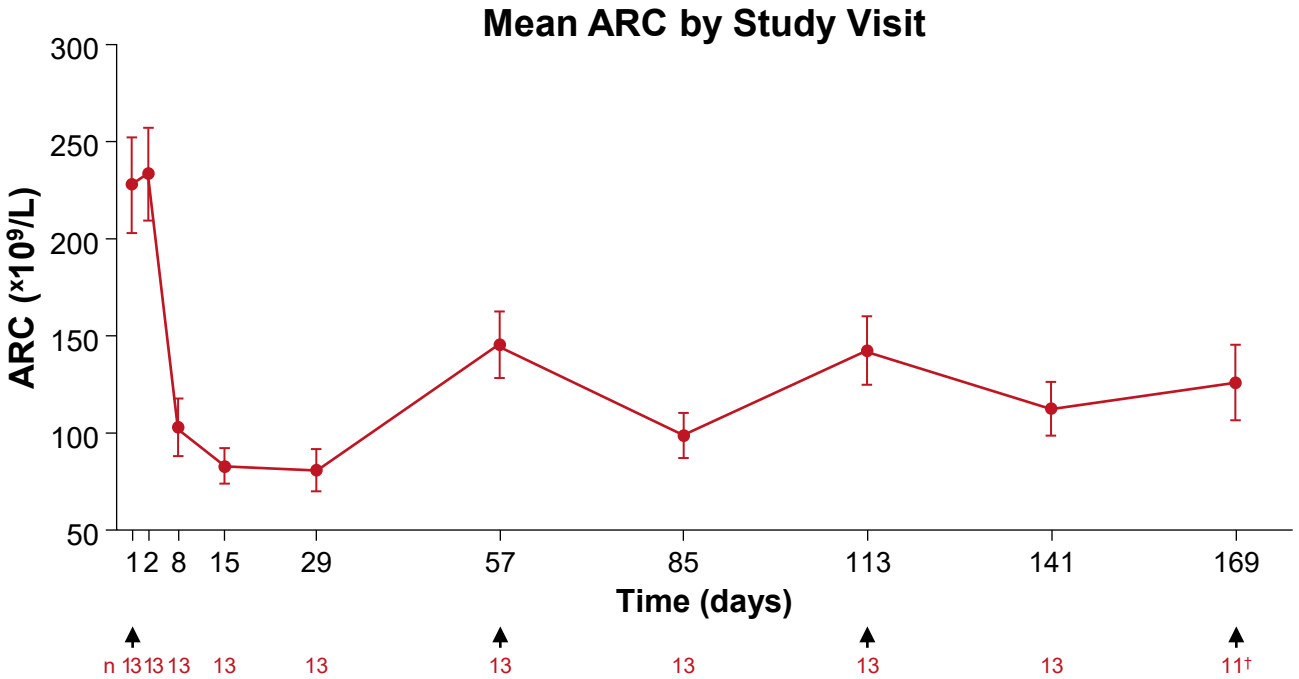
Dose-dependent Improvement in Hemoglobin Levels Following the Addition of OMS906 to Ravulizumab



- Greater magnitude and durability of response observed with the 5 mg/kg dose
- Consistent with the expected PK/PD profile of OMS906

*N=11 at day 169 following discontinuation due to a SAE. Response is defined as an increase in Hgb levels ≥2.0 g/dL. Arrows indicate OMS906 administration. Each timepoint depicts a study visit.
Hgb, hemoglobin; PD, pharmacodynamic; PK, pharmacokinetic; SAE, serious adverse event.

The Addition of OMS906 to Ravulizumab Also Resulted in Rapid and Sustained Reductions in ARC* in Patients With PNH



- At Day 29, mean ARC decreased by 146.43 $\times 10^9$/L (N=13; *P*<0.0001)
- At Day 169, mean ARC decreased by 115.31 $\times 10^9$/L (N=11; *P*=0.0001)

*ARC, absolute reticulocyte count. †N=11 at day 169 following 1 discontinuation due to a SAE and 1 patient's missing value. Arrows indicate OMS906 administration. Each timepoint depicts a study visit.
PNH, paroxysmal nocturnal hemoglobinuria; SAE, serious adverse event.

The Addition of OMS906 to Ravulizumab Was Safe and Well Tolerated in Patients With PNH

- Treatment-related AEs were observed in 38.5% of patients and were mostly mild–moderate grade
- No patients met the criteria for clinical breakthrough hemolysis*
- 1 SAE of increased ALT (intermittent and significant elevations since 2011) led to treatment discontinuation
- No MAVEs, meningococcal infections, or deaths were observed

TEAEs in ≥10% of Patients	n (%)
Headache	7 (53.8)
Fatigue	4 (30.8)
Oropharyngeal pain	4 (30.8)
Cough	3 (23.1)
Thrombocytopenia	3 (23.1)
Abdominal discomfort	2 (15.4)
Arthralgia	2 (15.4)
Back pain	2 (15.4)
COVID-19	2 (15.4)
Cystitis	2 (15.4)
Extravascular hemolysis	2 (15.4)
Hemoglobin decreased	2 (15.4)
Nasal congestion	2 (15.4)
Nasopharyngitis	2 (15.4)
Neutropenia	2 (15.4)

*Defined as ≥1 new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin reduction of ≥2 g/dL], major adverse vascular event [including thrombosis. dysphagia or erectile dysfunction) in the presence of elevated LDH ≥2×ULN after prior reduction of LDH to <1.5×ULN on treatment.
AE, adverse event; ALT, alanine transaminase; COVID-19, coronavirus disease 2019; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; PNH, paroxysmal nocturnal hemoglobinuria; SAE, serious adverse event; ULN, upper limit of normal.

Summary

- MASP-3 is an upstream activator of the alternative pathway and a novel target for PNH treatment
- In this pre-specified interim analysis, adjunctive treatment with OMS906 (zaltenibart), a MASP-3 inhibitor, was well tolerated and demonstrated preliminary efficacy in patients with PNH who were experiencing substantial extravascular hemolysis on ravulizumab monotherapy
  - The addition of OMS906 to a C5 inhibitor appeared to be safe and well tolerated
  - Treatment resulted in rapid improvement in Hgb and a reduction in ARC
  - Greater magnitude and durability of response was observed at the 5 mg/kg dose than at the 3 mg/kg dose
  - Following treatment with OMS906, no patients required transfusions
  - Ten of 12 patients (83%) are in the monotherapy stage of the study on OMS906 alone
- These results demonstrate that OMS906 is effective in controlling hemolysis, including extravascular hemolysis in patients with PNH, consistent with the mechanism of proximal inhibition

ARC, absolute reticulocyte count; Hgb, hemoglobin; MASP-3, mannan-binding lectin-associated serine protease 3; PNH, paroxysmal nocturnal hemoglobinuria.

Future Directions

- Responders are now progressing into the monotherapy (OMS906 alone) phase of this study and are showing sustained responses
- The observed favorable safety and efficacy profile of OMS906, an upstream alternative pathway inhibitor, supports further development as a monotherapy agent in the treatment of PNH
- Clinical as well as pharmacokinetic and pharmacodynamic data from patients in the two current clinical trials will be used to select the optimal dose for maximizing the extent and durability of response
  - Also see poster #P834 *Clinical Pharmacology of OMS906, a Potent Inhibitor of MASP-3 and the Alternative Pathway of Complement Activation*

Scan the QR code to obtain a copy of content*

*Copies obtained through this QR code are for personal use only and may not be reproduced.
PNH, paroxysmal nocturnal hemoglobinuria.

Acknowledgments and Disclaimer

Thank you to the patients, site staff, and investigators

ACKNOWLEDGMENTS

- This study was sponsored by Omeros Corporation (Seattle, WA)
- Study sites were from UK, Switzerland, and Germany
- Medical writing support was provided by AMICULUM USA and funded by Omeros Corporation (Seattle, WA)
- Hematology experts: Prof Ilene Weitz (Keck-USC School of Medicine, Los Angeles), Dr Jonathan Sive (University College London Hospital) and Dr Manos Nikolousis (Athens University Medical Centre)

DISCLAIMER

- OMS906 is an investigational agent and has not been approved by any regulatory agency