OMS906, a Novel Alternative Pathway MASP-3 Inhibitor, Normalizes Hemoglobin Levels and Increases Clone Size in Treatment-Naïve PNH Patients

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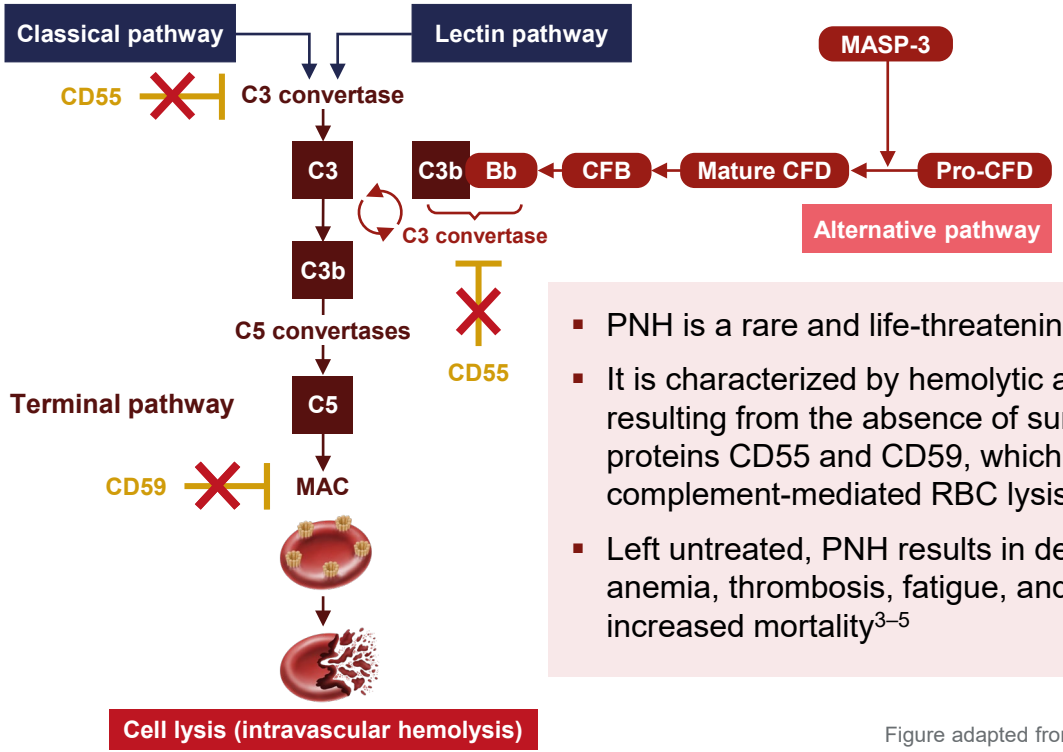
Clinical Presentation of PNH is Driven by Intravascular Hemolysis due to Dysregulation of the Complement System



- PNH is a rare and life-threatening disorder[1–3]
- It is characterized by hemolytic anemia resulting from the absence of surface proteins CD55 and CD59, which regulate complement-mediated RBC lysis[1–3]
- Left untreated, PNH results in debilitating anemia, thrombosis, fatigue, and increased mortality[3–5]

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

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; RBC, red blood cell.

1. Risitano AM *et al. Front Immunol* 2019;10:1157. **2.** Notaro R *et al. N Engl J Med* 2022;387:160–6. **3.** Risitano AM *et al. Immunol Rev* 2023;313:262–78. **4.** Loschi M *et al. Am J Hematol* 2016;91:366–70. **5.** Fattizzo B *et al. J Blood Med* 2022;13:327–35. **6.** Belcher JD *et al. Transl Res* 2022;249:1–12.

Terminal Complement Inhibition in PNH Inhibits Intravascular Hemolysis but Inevitably Leads to Extravascular Hemolysis[1,2]

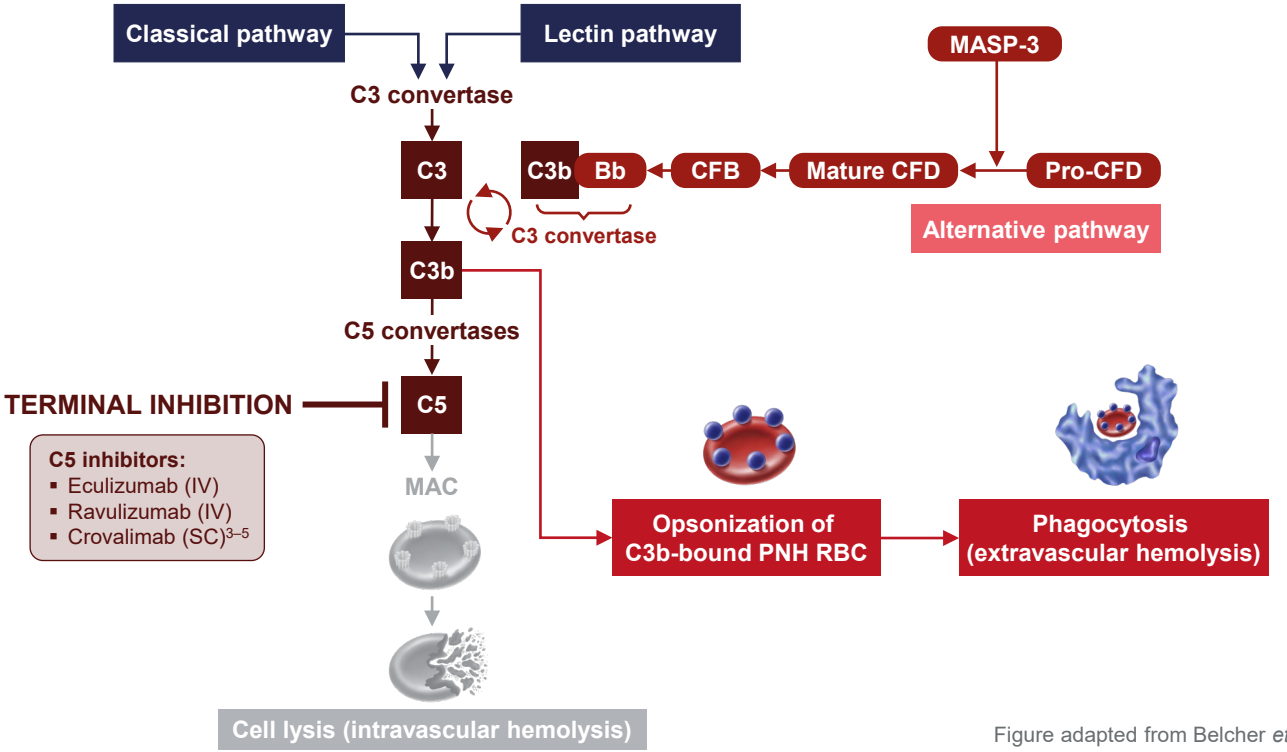
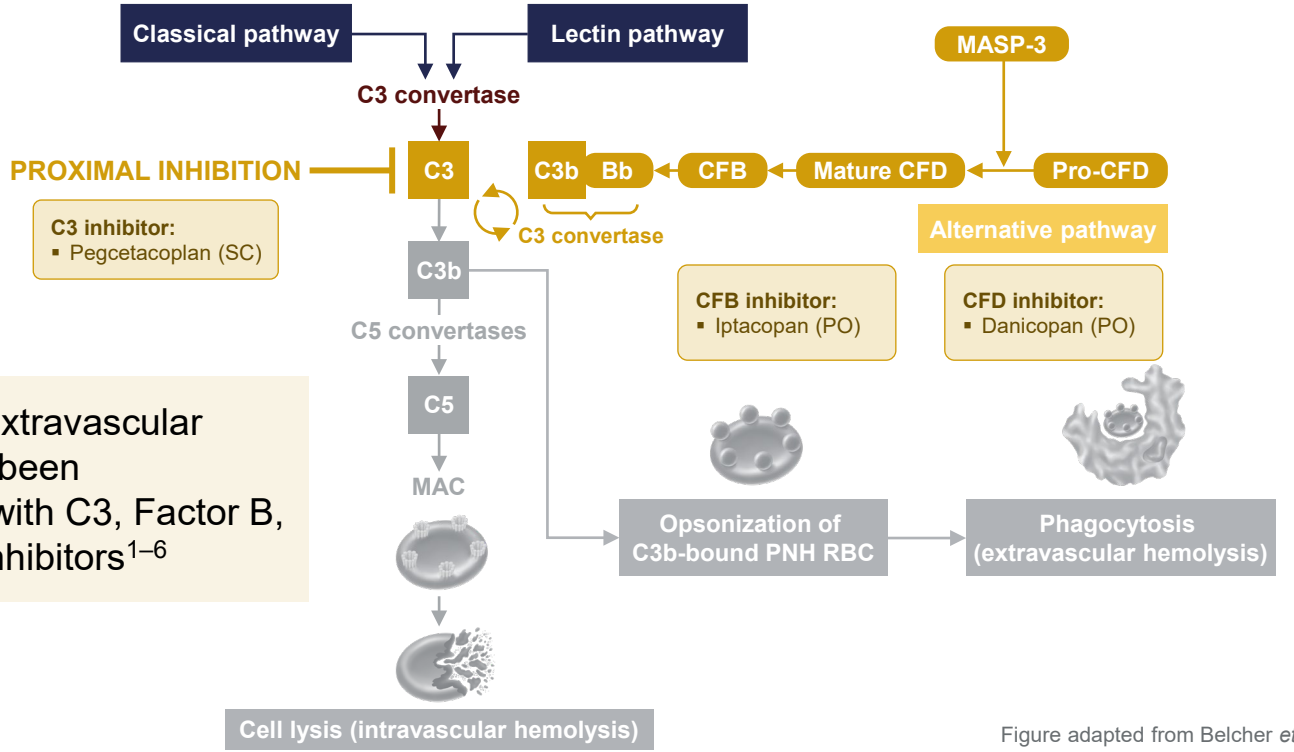


Figure adapted from Belcher *et al* (2022)[6]

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.** Kulasekararaj A *et al. HemaSphere* 2023;7(S3):S183. **5.** Chang A *et al. HemaSphere* 2023;7(S3):P785. **6.** Belcher JD *et al. Transl Res* 2022;249:1–12.

Proximal Inhibition of the Alternative Pathway Blocks Intravascular Hemolysis and Prevents Extravascular Hemolysis[1,2]



- Prevention of extravascular hemolysis has been demonstrated with C3, Factor B, and Factor D inhibitors[1–6]

Figure adapted from Belcher *et al* (2022)[7]

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, orally; 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.** Peffault de Latour P *et al. Blood* 2022;140(S2):LBA-2. **4.** Risitano AM *et al*. 49th Annual Meeting of the EBMT 2023; April 23–26, 2023; Paris: OS12-06. **5.** Risitano AM *et al. HemaSphere* 2023;7(S3):S182. **6.** Peffault de Latour P *et al. HemaSphere* 2023;7(S3):P774. **7.** Belcher JD *et al. Transl Res* 2022;249:1–12.

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

- Mannan-binding lectin-associated serine protease-3 (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]

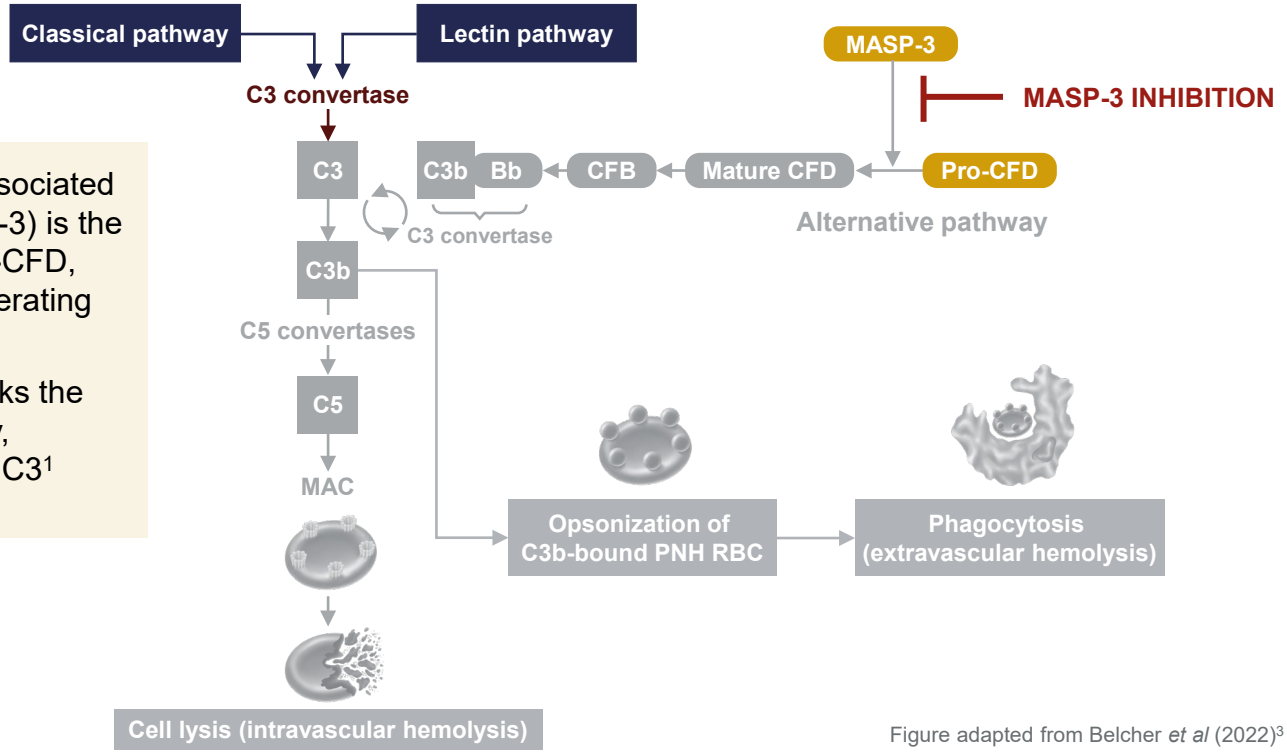


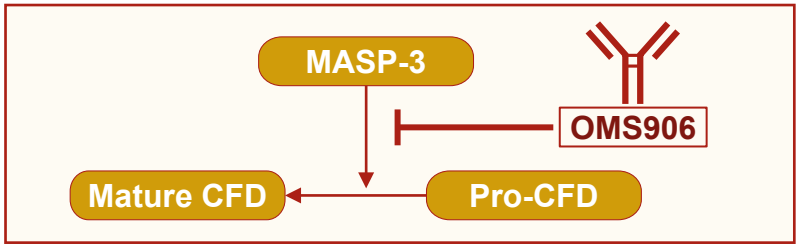
Figure adapted from Belcher *et al* (2022)[3]

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; RBC, red blood cell.

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 Selectively Targets MASP-3

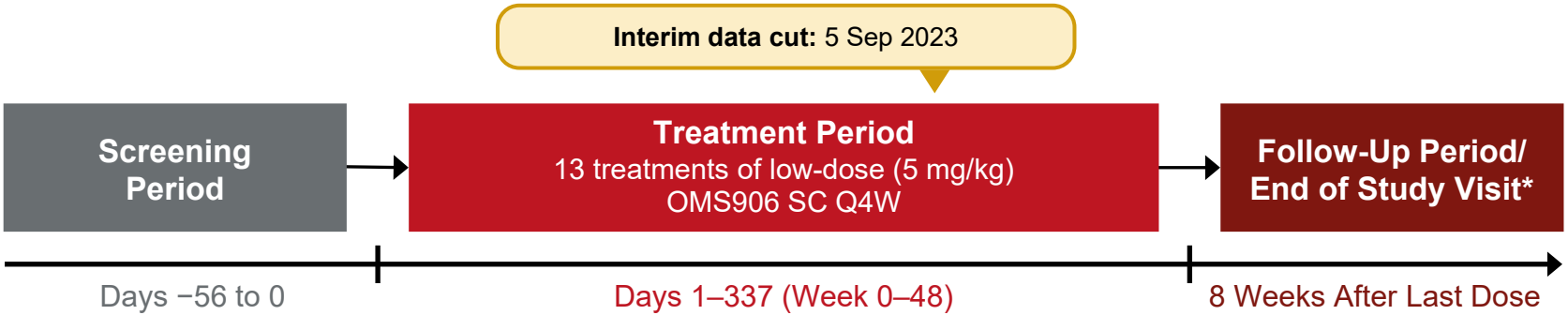
- OMS906 is a highly selective humanized IgG4 mAb that binds to and inhibits MASP-3[1,2]
- It can be administered SC or IV:[2]
  - $T_{½}$ (geometric mean): 239–406 h (SC)
  - $T_{½}$ (geometric mean): 94–399 h (IV)
- In a Phase 1 study in healthy subjects, OMS906 was well tolerated, with 5 mg/kg SC providing substantial MASP-3 inhibition through Day 42[2]



CFD, complement Factor D; IgG, immunoglobulin G; IV, intravenous; mAb, monoclonal antibody; MASP-3, mannan-binding lectin-associated serine protease 3; SC, subcutaneous; $T_{½}$, terminal elimination half-life.

1. Cummings WJ *et al. Mol Immunol* 2022;150:145. **2.** Griffin M *et al. HemaSphere* 2023;7(S3):P787.

Study Design for the Treatment-Naïve Cohort in an Ongoing Phase 1b Trial of OMS906 (NCT05889299; EudraCT 2022-002450-22)



Key Inclusion Criteria:

- Adults with confirmed PNH diagnosis by flow cytometry (RBC clone size >10%)
- Complement inhibitor treatment naïve†
- Hgb <10.5 g/dL
- LDH >1.5 × ULN
- *Neisseria meningitidis* vaccination

Primary Endpoint:

- Safety and tolerability

Key Secondary Endpoints:

- Preliminary efficacy by effect on hemolysis and anemia:
  - Change from baseline in Hgb and LDH levels, absolute reticulocyte count, RBC transfusion burden
  - Proportion of patients achieving Hgb ≥12 g/dL or increase in Hgb ≥2 g/dL

*If patient discontinues from study for any reason; †Patients treated with any complement pathway inhibitor within 6 months prior to screening were excluded.
Hgb, hemoglobin; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; Q4W, every 4 weeks; RBC, red blood cell; SC, subcutaneous; ULN, upper limit of normal.

Patient Treatment Status

- This study enrolled 11 patients between 20 December 2022 and 1 May 2023
  - Interim analysis data cut: 5 September 2023
- All 11 patients have received OMS906 (5 mg/kg SC, “low dose”)

No. of Patients	Doses Received
11	≥4
7	≥6

- This study provided treatment access for patients with PNH who had no other options available

PNH, paroxysmal nocturnal hemoglobinuria; SC, subcutaneous

The Majority of Patients Received RBC Transfusions in the 12 Months Prior to OMS906 Treatment

	OMS906 5 mg/kg SC N=11	
Baseline demographics	**Mean (SD)**	**Median (range)**
Age, years	41.0 (15.6)	37 (27–72)
Weight, kg	72.4 (13.3)	66.5 (56–95)
Female, n (%)	6 (55)	
Caucasian, n (%)	11 (100)	
PNH disease characteristics	**Mean (SD)**	**Median (range)**
PNH clone size, %	93 (0.13)	97 (55–99)
Patients receiving RBC transfusions,* n (%)	7 (64)	
Patients receiving steroids for PNH, n (%)	6 (55)	
Laboratory marker at baseline	**Mean (SD)**	**Median (range)**
Hgb, g/dL	7.0 (2.2)	6.4 (3.9–10.4)
LDH, U/L	1835 (749)	1831 (905–3480)
Absolute reticulocytes, $\times 10^9$/L	183 (71)	162 (107–307)

	OMS906 5 mg/kg SC N=11
Medical history, n (%)	
Iron deficiency	6 (55)
Chronic kidney disease	3 (27)
MDS	2 (18)
Aplastic anemia	2 (18)
Folate deficiency	3 (27)
B12 deficiency	3 (27)
Concomitant medications, n (%)	
Rivaroxaban	10 (91)
Ursodiol	8 (73)
Enoxaparin	4 (36)
Iron	4 (36)
Folate	3 (27)
Vitamin B12	3 (27)

Data shown are from interim data cut as of 5 September 2023. *In the 12 months prior to OMS906 treatment.
Hgb, hemoglobin; LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; SC, subcutaneous; SD, standard deviation.

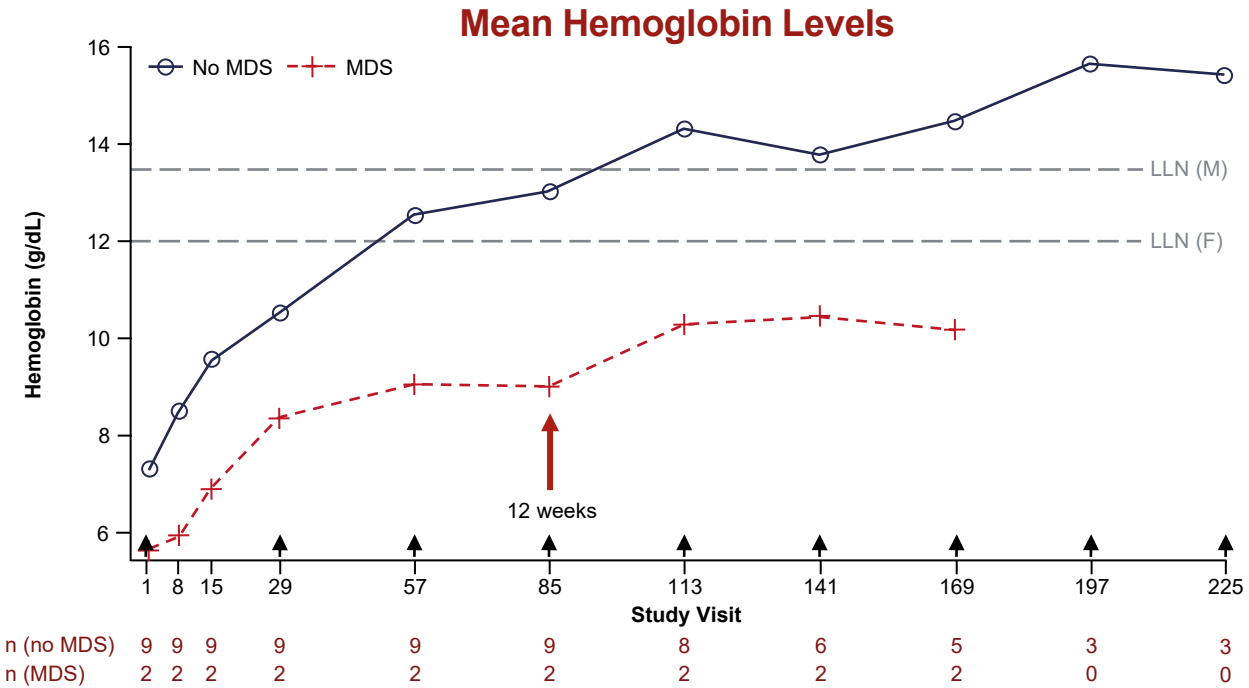
OMS906 Treatment Was Well Tolerated in Patients with PNH

Adverse Events in ≥20% of Patients	n (%)	CTCAE Grade
Itching	3 (27)	All Grade 1
Increased thrombocytopenia	4 (36)	1 patient Grade 1* 2 patients Grade 2* 1 patient Grade 3†
Transient neutropenia	3 (27)	3 patients Grade 3

- All patients with reported cytopenia had evidence of underlying bone marrow failure
- No clinical breakthrough hemolysis
- No MAVEs
- No treatment-related SAEs, discontinuations, or deaths

Data shown are from interim data cut as of 5 September 2023. *Received iron therapy; †Had pre-existing Grade 3 thrombocytopenia and myelodysplastic syndrome.
CTCAE, Common Terminology Criteria for Adverse Events; MAVE, major adverse vascular event; PNH, paroxysmal nocturnal hemoglobinuria; SAE, serious adverse event.

Treatment with Low-Dose OMS906 Rapidly Improved Hemoglobin Levels



At 12 weeks, mean increase in Hgb was 5.3 g/dL from baseline (P<0.001)

- ↑5.7 g/dL (patients without MDS)
- ↑3.4 g/dL (patients with MDS)

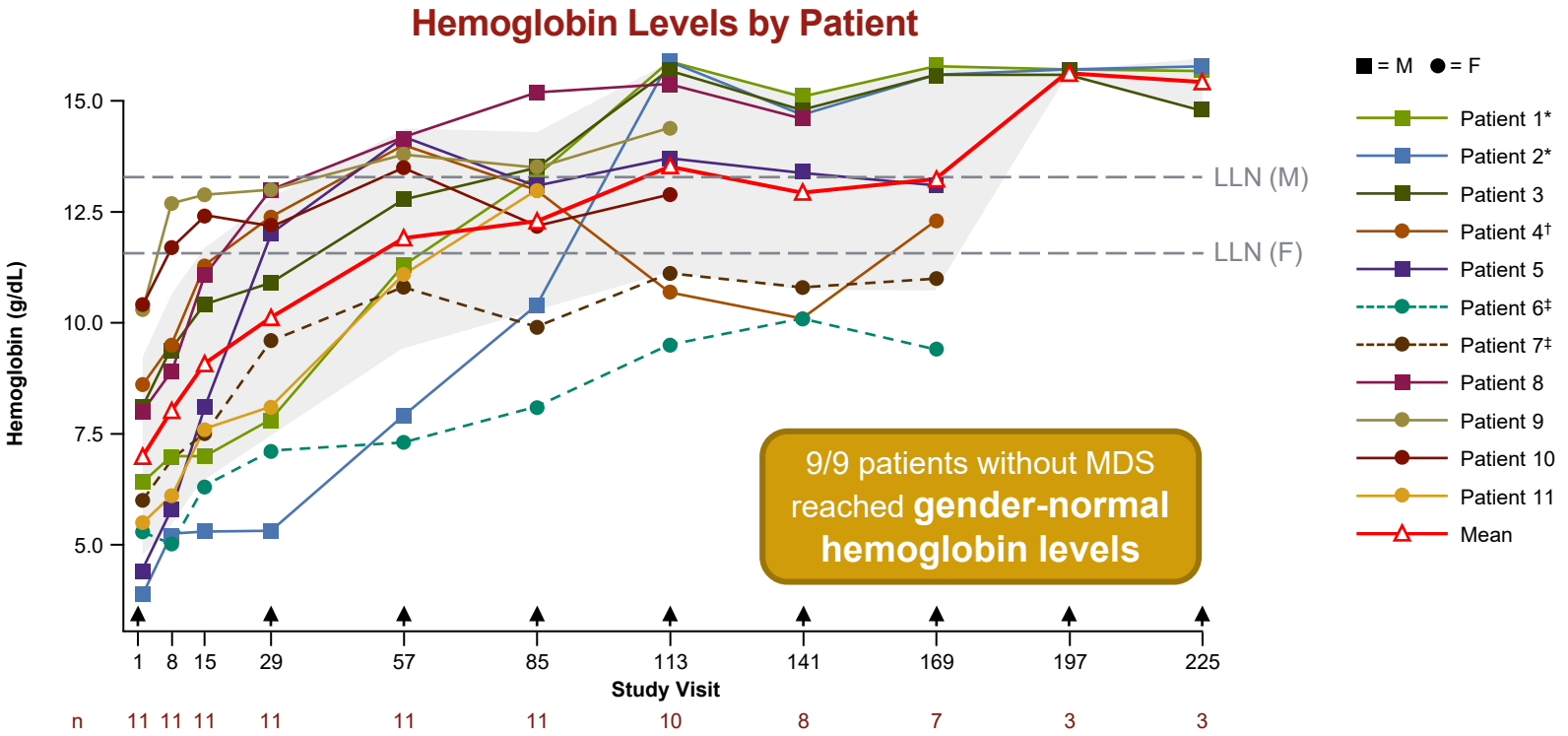
11/11 patients had an increase in **Hgb ≥2 g/dL**

9/9 patients without MDS achieved **Hgb ≥12 g/dL**

- Patients without MDS had more rapid improvement in hemoglobin levels after treatment with low-dose OMS906
- No patients required transfusions following initiation of OMS906 treatment

Data shown are from interim data cut as of 5 September 2023. *P* values are for testing change from baseline using t-test; *P* values may not be valid for small N.
Black arrows indicate OMS906 administration following laboratory marker collection.
F, female; Hgb, hemoglobin; LLN, lower limit of normal; M, male; MDS, myelodysplastic syndrome.

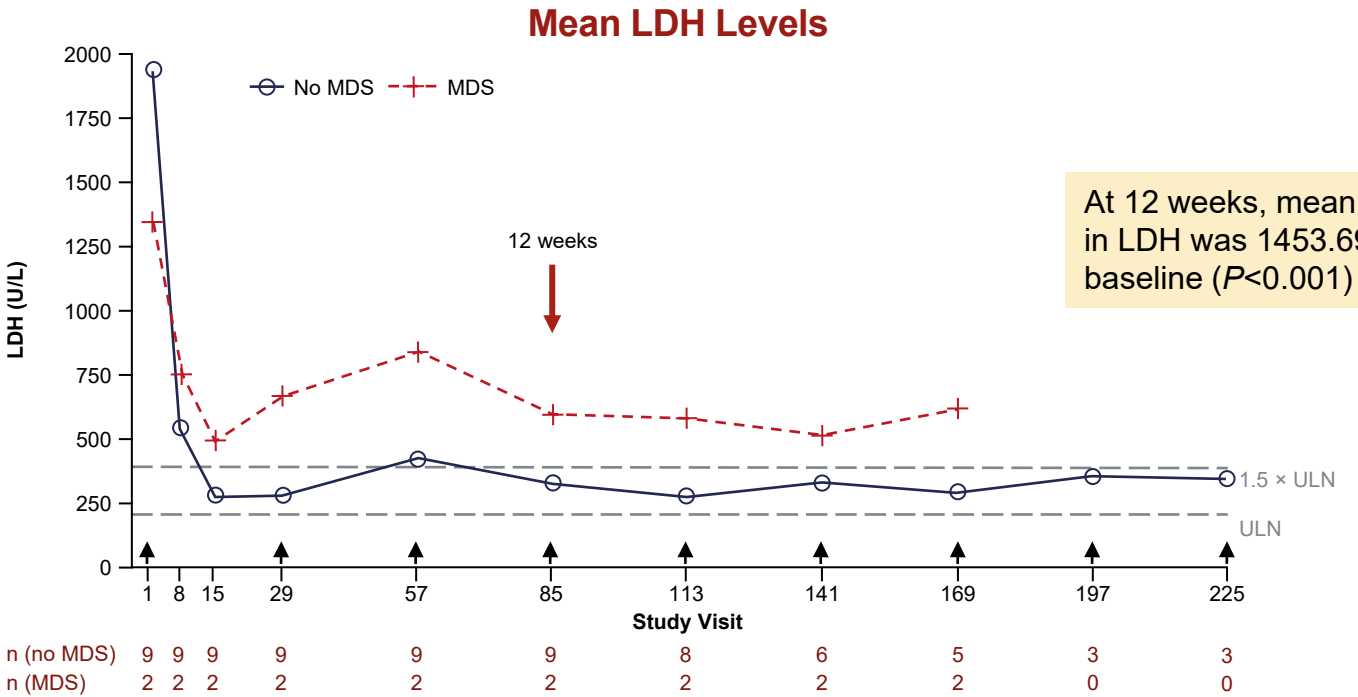
Treatment with Low-Dose OMS906 Rapidly Improved Hemoglobin Levels



- No patients required transfusions following initiation of OMS906 treatment

Data shown are from interim data cut as of 5 September 2023. Black arrows indicate OMS906 administration following laboratory marker collection. Grey shading represents variance. *Patients 1 and 2 have aplastic anemia; †Patient 4 had hip arthroplasty of right hip at Day100; ‡Patients 6 and 7 have MDS; F, female; LLN, lower limit of normal; M, male; MDS, myelodysplastic syndrome.

Treatment with Low-Dose OMS906 Reduced LDH Levels

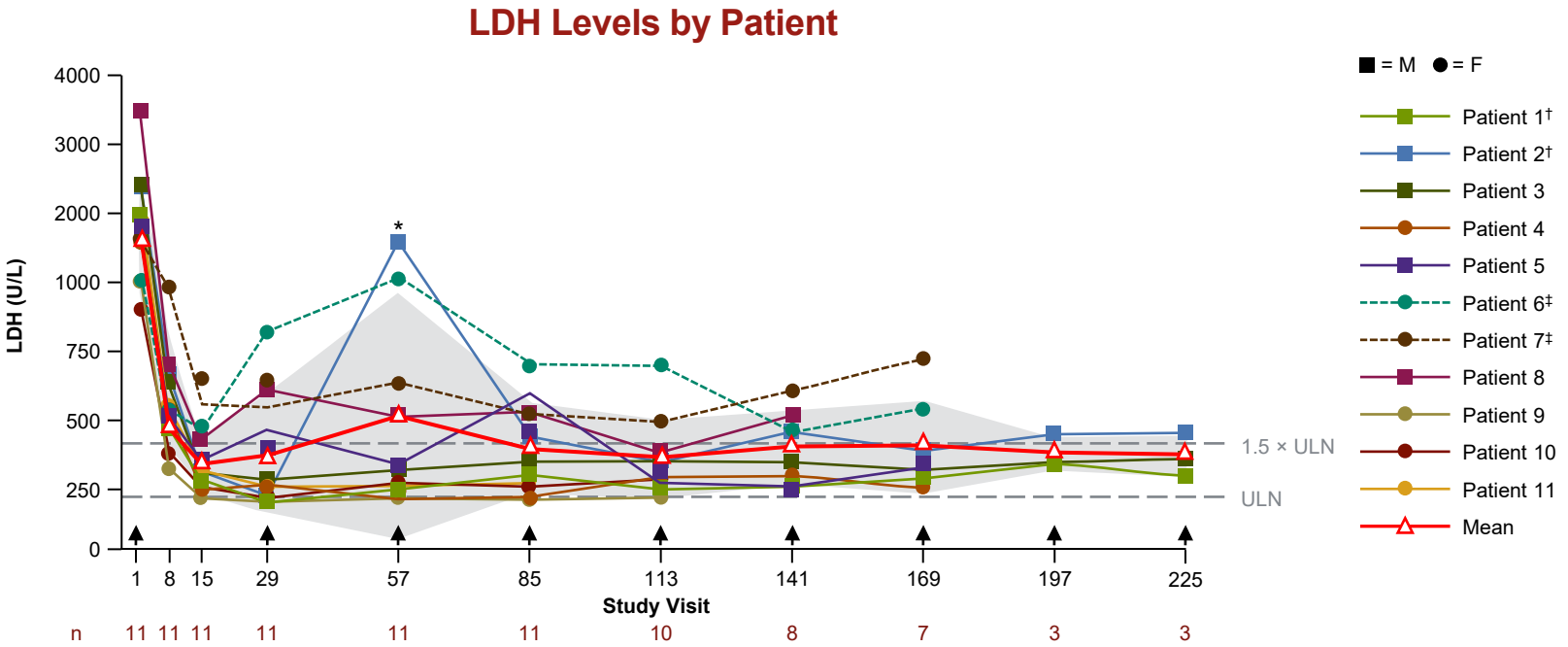


At 12 weeks, mean reduction in LDH was 1453.69 U/L from baseline (*P*<0.001)

- PK and PD from these patients will help inform planned dose escalation to achieve once-quarterly dosing

Data shown are from interim data cut as of 5 September 2023. *P* values are for testing change from baseline using t-test; *P* values may not be valid for small N.
Black arrows indicate OMS906 administration following laboratory marker collection.
LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome; PD, pharmacodynamics; PK, pharmacokinetics; ULN, upper limit of normal.

Treatment with Low-Dose OMS906 Reduced LDH Levels

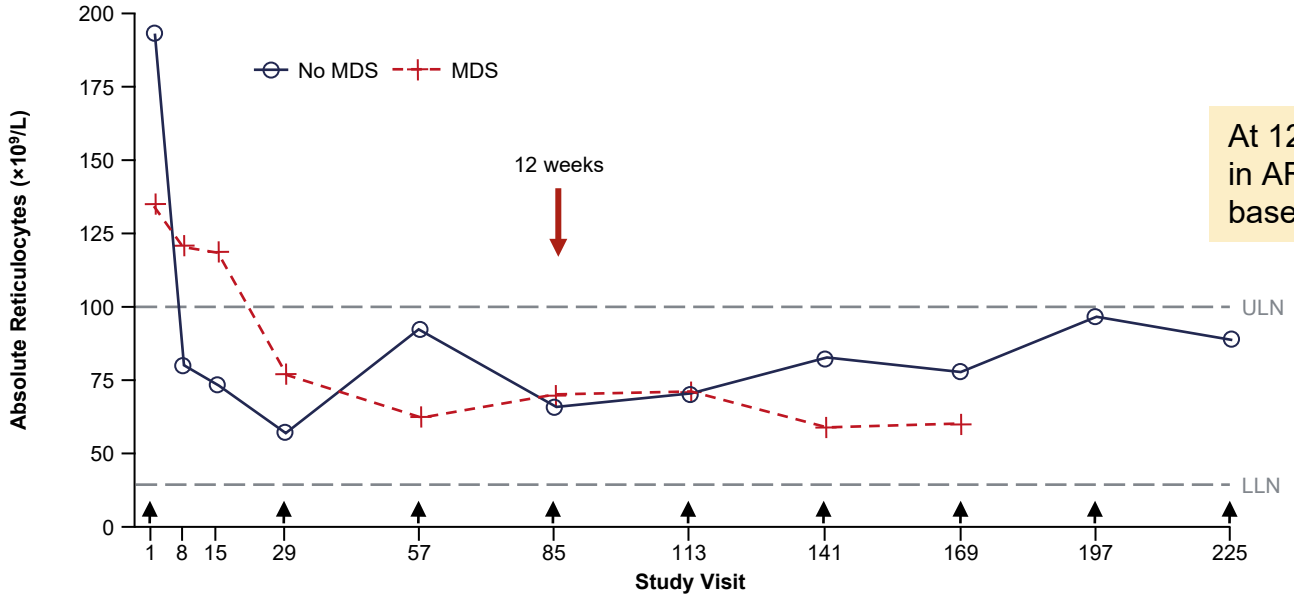


- Three patients had increases in LDH suggesting initiation of hemolysis at the end of a dosing period, although hemoglobin was not reduced in any of these patients
- PK and PD from these patients will help inform planned dose escalation to achieve once-quarterly dosing

Data shown are from interim data cut as of 5 September 2023. Black arrows indicate OMS906 administration following laboratory marker collection. Grey shading represents variance. *Patient 2 had mild COVID-19 infection prior to Day 57 visit; †Patients 1 and 2 have aplastic anemia; ‡Patients 6 and 7 have MDS.
F, female; LDH, lactate dehydrogenase; M, male; MDS, myelodysplastic syndrome; PD, pharmacodynamic; PK, pharmacokinetic; ULN, upper limit of normal.

Absolute Reticulocyte Count Decreased Overall with OMS906 Treatment

Mean Absolute Reticulocyte Count

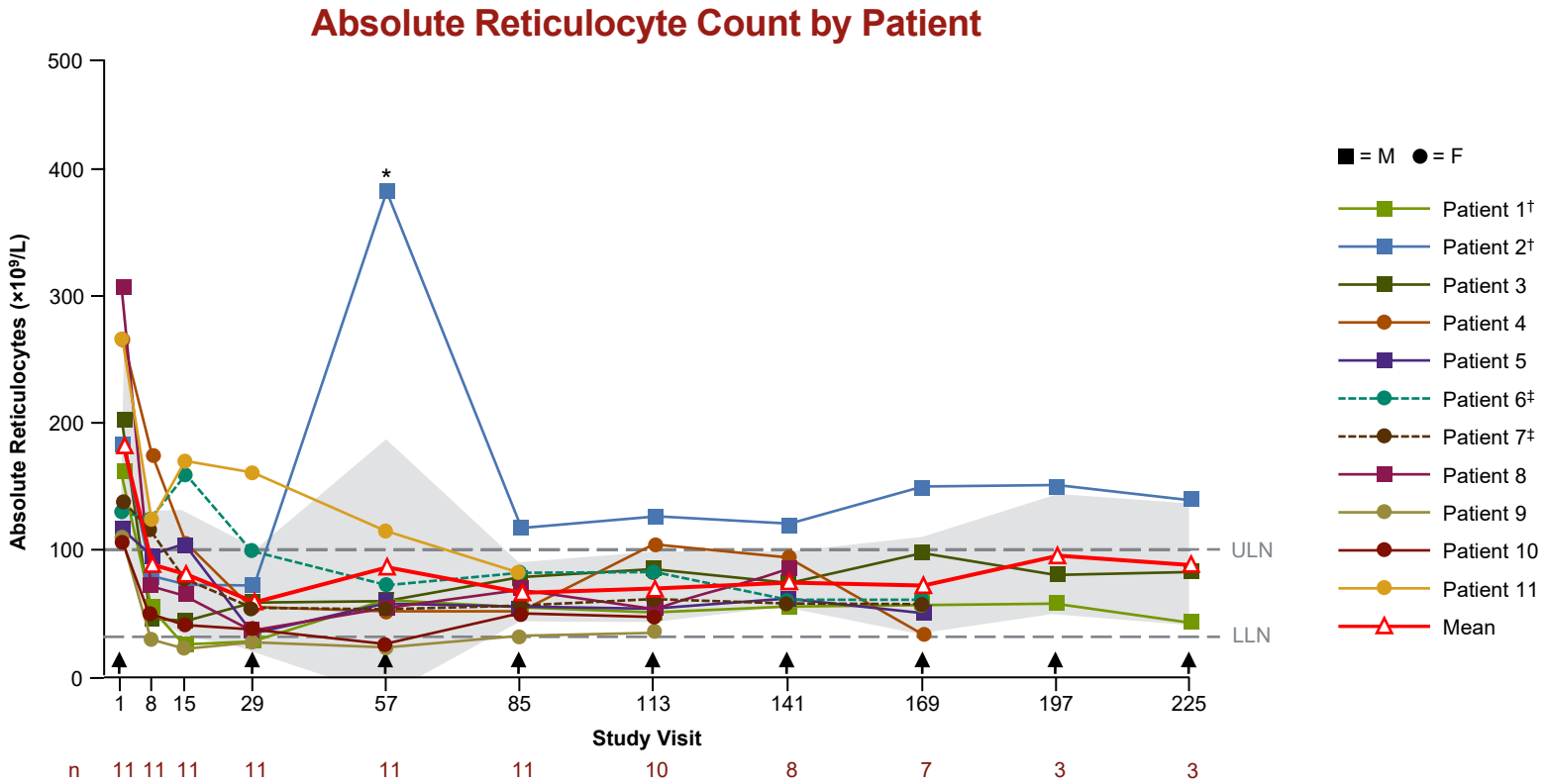


At 12 weeks, mean reduction in ARC was 116 x 10^9/L from baseline (P<0.001)

- Mean absolute reticulocyte counts were reduced from baseline by 92–122 × 10^9/L at all timepoints

Data shown are from interim data cut as of 5 September 2023. *P* values are for testing change from baseline using t-test; *P* values may not be valid for small N.
Black arrows indicate OMS906 administration following laboratory marker collection.
ARC, absolute reticulocyte count; LLN, lower limit of normal; MDS, myelodysplastic syndrome; ULN, upper limit of normal.

Absolute Reticulocyte Count Decreased Overall with OMS906 Treatment



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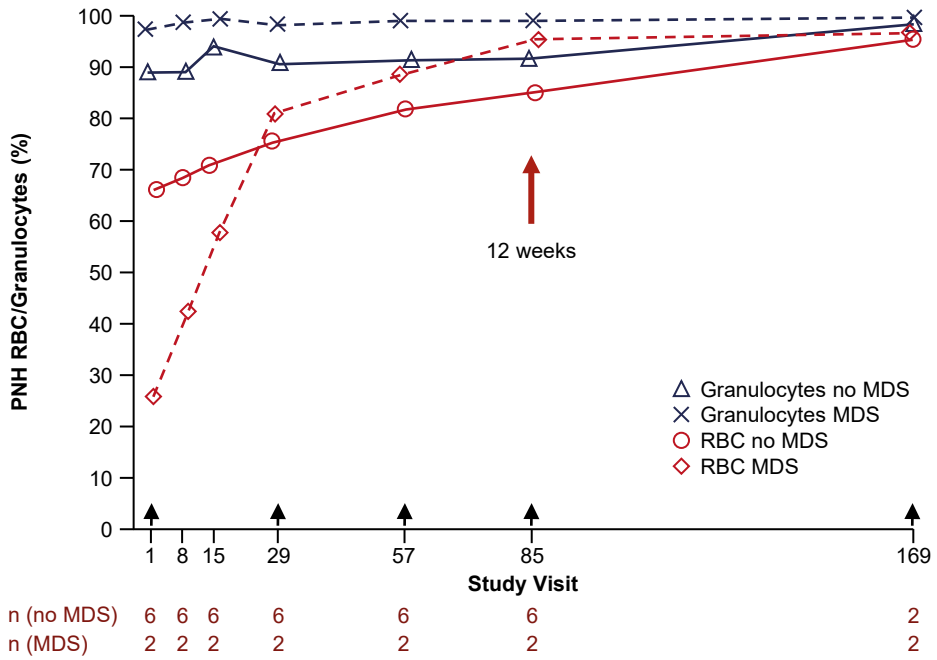
PNH RBC Clone Size Increased Over Time with OMS906 Treatment, Indicating Protection of the RBCs

Mean PNH RBC and Granulocyte Clone Size



- At week 12, PNH RBC clone size increased to a mean of 87.6% (range 67.4–96.4%) from a mean baseline level of 56.1% (*P* = 0.011)
- Increase was greater in the two patients with MDS

PNH RBC Clone Size

MDS	Baseline	Day 29 (change from baseline)	Day 85 (change from baseline)
No (n=6)	66.2%	75.8% (+9.6%)	85.0% (+18.8%)
Yes (n=2)	25.9%	80.9% (+55%)	95.4% (+69.5%)

Data shown are from interim data cut as of 5 September 2023. *P* values are for testing change from baseline using t-test; *P* values may not be valid for small N.
Black arrows indicate OMS906 administration following laboratory marker collection.
MDS, myelodysplastic syndrome; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell.

Conclusions

- MASP-3 is an activator of the alternative pathway and a novel target for PNH treatment
- OMS906, a MASP-3 inhibitor, showed promising efficacy in this interim analysis:
  - Normalization of **Hgb** (9/11 patients) was achieved with monthly SC dosing without clinical breakthrough hemolysis
  - Normalization of **LDH** (8/11 patients <1.5 × ULN), **ARC** (10/11 patients), and **transfusion independence** (11/11 patients) were achieved
  - Patients with MDS demonstrated notable response to OMS906, though to a lesser extent than patients without MDS
- OMS906 continues to be well tolerated with no safety signals of concern
- OMS906 dose escalation guided by the PK/PD of patients with subclinical hemolysis is underway to inform achievement of quarterly dosing
- Further evaluation of OMS906 for PNH will explore GPI-deficient patients who have a suboptimal response to C5 inhibitors or are complement inhibitor treatment naïve
- A C5-switchover PNH trial is fully enrolled in sites in UK, Germany, and Switzerland; additional alternative pathway-mediated indications are being evaluated

ARC, absolute reticulocyte count; GPI, glycosylphosphatidylinositol; Hgb, hemoglobin; LDH, lactate dehydrogenase; MASP-3, mannan-binding lectin-associated serine protease 3; MDS, myelodysplastic syndrome; PD, pharmacodynamics; PK, pharmacokinetics; PNH, paroxysmal nocturnal hemoglobinuria; SC, subcutaneous.