Monotherapy Treatment with Zaltenibart (OMS906), an Alternative Pathway MASP-3 Inhibitor, Improved Key Hematologic Parameters in Patients with PNH with a Suboptimal Response to Ravulizumab: Interim Results from a Phase 2 Proof-of-Concept Study

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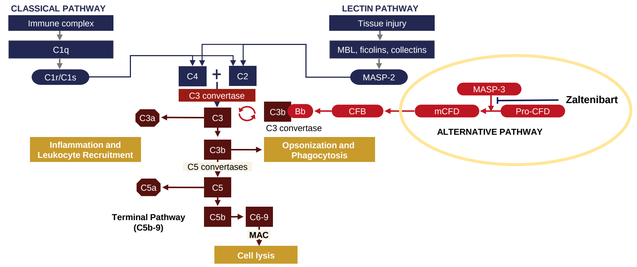
BACKGROUND

- Mannan-binding lectin-associated serine protease-3 (MASP-3) is the most upstream activator of complement factor D (CFD) and regulator of the alternative pathway of complement[1,2] (**Figure 1**)
- Inhibition of MASP-3 could provide therapeutic benefit in a variety of alternative pathway-mediated diseases, including paroxysmal nocturnal hemoglobinuria (PNH), a rare and life-threatening disorder involving complement dysregulation that leads to hemolytic anemia[1]
- Zaltenibart (OMS906) is a highly selective humanized IgG4 mAb that binds to and inhibits MASP-3, providing proximal inhibition of alternative pathway activity[3,4]
- In the first stage of this single-arm, open-label, Phase 2 proof-of-concept study (NCT05972967), zaltenibart in addition to ravulizumab was well tolerated and demonstrated efficacy in patients with PNH who were experiencing substantial extravascular hemolysis (EVH) on ravulizumab monotherapy[5]
- In the second stage of the study, patients discontinued ravulizumab and continued on monotherapy with zaltenibart, provided the patient met clinical response criteria and/or the Investigator determined that this was clinically appropriate; here we report results from this stage of the study

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



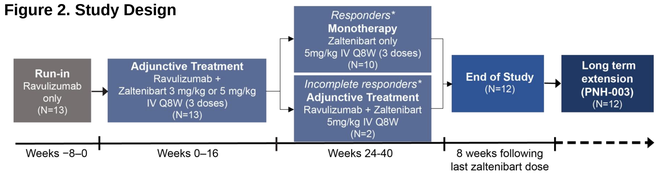
OBJECTIVE

- To evaluate the safety, tolerability, and preliminary efficacy of zaltenibart as monotherapy in patients with PNH with a suboptimal response to ravulizumab

METHODS

- This was a single-arm, open-label, Phase 2 proof-of-concept clinical trial (NCT05972967)
- Patients with a confirmed PNH diagnosis by flow cytometry (RBC and/or granulocyte clone size >10%) and suboptimal response to ravulizumab (baseline Hgb <10.5 g/dL despite at least 4 months of ravulizumab) were eligible for the study
- Primary endpoints were safety and tolerability; secondary endpoints included change from baseline in Hgb and ARC, number of RBC transfusions, and PK/PD measures
- Patients continued ravulizumab at weeks 0, 8, and 16 with concurrent zaltenibart dosing (3mg/kg IV Q8W or 5mg/kg IV Q8W); clinical responders (patients with a Hgb increase ≥ 2.0 g/dL) to the combination at week 24 (study day 169) transitioned to 5mg/kg IV Q8W zaltenibart monotherapy or continued treatment with the combination (**Figure 2**)
- Here we report results from the monotherapy stage of the study (weeks 24-40, d169-337)

Figure 2. Study Design



*Response is defined as an increase in Hgb levels ≥2.0 g/dL. Incomplete responders had a clinical response with Hgb increase <2.0 g/dL.

RESULTS

Baseline Demographics

- 13 patients with PNH (**Table 1**; 7 female, mean age 53.2 years [range 23-80]) who had a suboptimal response to ravulizumab initially enrolled and received adjunctive treatment with zaltenibart
- 12 entered the monotherapy stage and 12 completed the study

Table 1. Baseline Demographics and Clinical Characteristics

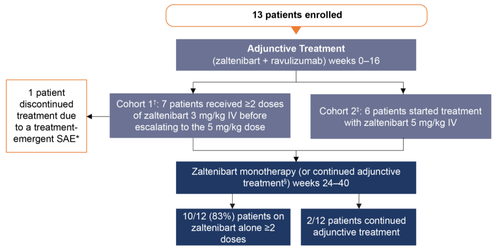
Baseline demographics and clinical characteristics	Enrolled patients N=13	
Baseline demographics	**Mean (SD)**	**Median (range)**
Age, years	53.2 (18.3)	52 (23–80)
Weight, kg	76.3 (17.3)	78 (55.6–115.2)
Female, n (%)	7 (53.8)	
Caucasian, n (%)	10 (76.9)	
PNH disease characteristics	**Mean (SD)**	**Median (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), ×10⁹/L	227.74 (88.55)	204.96 (105.3–407.5)
Medical history, n (%)		
Aplastic anemia	6 (46.2)	

*At least one transfusion within the 12 months prior to starting zaltenibart 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.

Results: Patient Disposition and Exposure

- 13 patients were enrolled and commenced adjunctive treatment; there was 1 early discontinuation (prior to d169) due to triggering Hy's law criteria* (not related to zaltenibart), and 12 completed the study
- Overall,1 patient received 3 doses of zaltenibart, 11 patients received 6 doses, and 1 patient received 7 doses (extra dose given for BTH)
  - 7 patients started on 3 mg/kg and transitioned to 5 mg/kg, 6 received 5mg/kg from study start, and all patients were on 5mg/kg at the end of the adjunctive stage on d169
- At d169, 12 patients transitioned to the second stage of the study (**Figure 3**)
  - 8 patients went straight to monotherapy (zaltenibart alone) and received 3 subsequent doses of zaltenibart
  - 2 patients continued on adjunctive treatment (3 subsequent doses of ravulizumab plus zaltenibart)
  - 2 patients switched from adjunctive treatment to monotherapy on d225 (receiving 2 subsequent doses of zaltenibart alone)

Figure 3. Patient Disposition



*Hy's law criteria defined as serum ALT or AST ≥ 3xULN and serum total bilirubin elevated to > 2xULN, without initial findings of cholestasis (elevated serum ALP). ‡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.

Results: Patient Response

- At the end of the adjunctive stage on d169, there were 9 complete responders (75%) and 3 incomplete responders
- At the end of the study on d337 (week 48), 9/12 patients (75%) were responders:
  - 1 patient, a non responder at d169, who continued on adjunctive therapy became a responder by end of study. Note: 1 patient who was a responder at d169 and d307 became an incomplete responder at d337
  - 1 patient who was an incomplete responder at the end of the adjunctive stage (d169) continued to be an incomplete responder at d337 due to an ongoing SAE of necrotizing otitis externa (NOE) and breakthrough hemolysis (BTH)
  - A second patient, initially a responder at d169, had BTH secondary to an eye infection (unrelated to treatment), and became an incomplete responder at d337. They received an additional dose of zaltenibart 5mg/kg IV on d309
- 10/12 (83%) of patients were transfusion-free following the monotherapy stage
  - Six patients (of 13) required RBC transfusions before the study

Results: Hemoglobin Levels

- In the adjunctive stage, patients experienced rapid and sustained improvements in Hgb from baseline (mean baseline = 8.98 g/dL; mean increase = 3.46 g/dL at day 169, N=12) (**Table 2**)
- These marked improvements in Hgb from baseline were maintained following transition to zaltenibart monotherapy on study day d169 (**Figure 4**)
- At the end of the study (EOS; d337), mean Hgb was 12.00 g/dL, a 2.83 g/dL increase from the study baseline (p=0.0006; N=12)

Figure 4. Mean Hgb by Study Visit

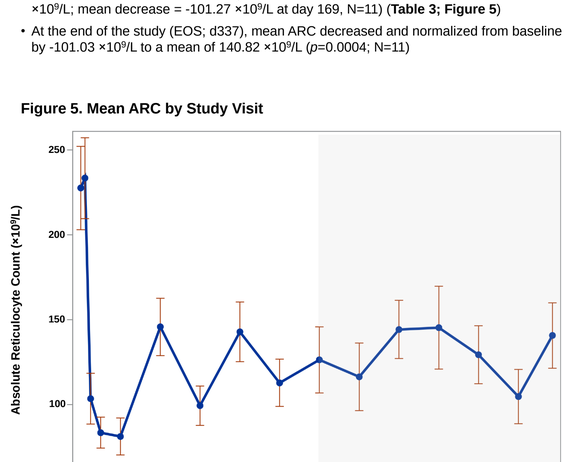


Table 2. Mean Hgb and Change from Baseline with Zaltenibart Treatment Through Adjunct and Monotherapy Stages

Mean Hgb (g/dL)	Baseline	Day 169	Day 337 (EOS)	Change from baseline at EOS
All patients, mean (SD)	8.98 (1.21) (n=13)	12.44 (1.42) (n=12)	12.00 (1.60) (n=12)	2.83 (2.04) (p=0.0006)
Zaltenibart monotherapy ≥2 doses, mean (SD)	9.13 (1.11) (n=10)	12.81 (1.24) (n=10)	11.95 (1.75) (n=10)	2.82 (2.22) (p=0.003)

Results: Absolute Reticulocyte Count Levels

- The addition of zaltenibart to ravulizumab also resulted in rapid and sustained reductions in ARC that were maintained during the monotherapy stage (mean baseline = 227.74 ×10⁹/L; mean decrease = -101.27 ×10⁹/L at day 169, N=11) (**Table 3; Figure 5**)
- At the end of the study (EOS; d337), mean ARC decreased and normalized from baseline by -101.03 ×10⁹/L to a mean of 140.82 ×10⁹/L (p=0.0004; N=11)

Figure 5. Mean ARC by Study Visit

Table 3. Mean ARC and Change from Baseline with Zaltenibart Treatment Through Adjunct and Monotherapy Stages

Mean ARC (x10⁹/L)	Baseline	Day 169	Day 337 (EOS)	Change from baseline at EOS
All patients, mean (SD)	227.74 (88.55) (n=13)	126.47 (64.66) (n=11)	140.82 (63.95) (n=11)	-101.03 (64.82) (p=0.0004)
Zaltenibart monotherapy ≥2 doses, mean (SD)	248.18 (91.04) (n=10)	130.37 (66.78) (n=10)	149.77 (67.95) (n=9)	-106.99 (70.94) (p=0.0019)

Results: Safety and Tolerability

- There was 1 treatment-related SAE due to necrotizing otitis externa
- TEAEs were observed in all 13 patients and were mostly of mild-moderate grade; TEAEs occurring in ≥10% of patients are reported in **Table 4**
  - During the monotherapy stage, the events of an ear infection and eye infection, each in a single patient, were associated with clinical BTH
  - Treatment-related AEs were reported in 6 patients **(Table 5)**
- There were no hypersensitivity type reactions
- No MAVEs, meningococcal infections, or deaths were reported
- Overall, zaltenibart appeared safe and was well tolerated

Table 4. TEAEs Occurring in >10% of Patients*

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

*By preferred term.

Table 5. Treatment-Related AEs*

Treatment-Related Adverse Events	n (%)
Any Event	6 (46.2)
Nasopharyngitis	1 (7.7)
Otitis externa	1 (7.7)
Leukopenia	1 (7.7)
Neutropenia	1 (7.7)
Thrombocytopenia	2 (15.4)
Headache	1 (7.7)
Back pain	1 (7.7)

SUMMARY AND CONCLUSIONS

- MASP-3, the most upstream regulator of the alternative pathway, is a novel target for the treatment of PNH
- In this study of PNH patients experiencing a suboptimal response to ravulizumab, adjunctive treatment and monotherapy with zaltenibart were well tolerated and improved Hgb and ARC levels and RBC transfusion independence, demonstrating strong efficacy responses and adequate control of PNH
- Patients continued to respond to zaltenibart 5mg/kg IV Q8W when administered as a single agent in the monotherapy stage of the study
- Overall, data from this Phase 2 clinical trial support the potential for zaltenibart as a monotherapy for treating PNH in patients with suboptimal responses to a C5 inhibitor

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DISCLAIMER

Zaltenibart is an investigational agent and has not been approved by any regulatory agency.

ABBREVIATIONS

AE, adverse event; ALT, alanine aminotransferase; AP, alternative pathway; ARC, absolute reticulocyte count; BTH, breakthrough hemolysis; CFB, complement factor B; CFD, complement factor D; EOS, end of study; EVH, extravascular hemolysis; Hgb, hemoglobin; IgG4, immunoglobulin G4; IV, intravenous; mAb, monoclonal antibody; LDH, lactate dehydrogenase; MASP-3, Mannan-binding lectin-associated serine protease-3; mCFD, mature complement factor D; PD, pharmacodynamics; PK, pharmacokinetics; PNH, paroxysmal nocturnal hemoglobinuria; proCFD, pro-complement factor D; Q8W, every 8 weeks; RBC, red blood cell; SAE, serious adverse event; SC, subcutaneous; TEAE, treatment-emergent adverse event.

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