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Alternative Pathway MASP-3 Inhibitor OMS906: Results From a First-in-Man Phase 1 Study in Healthy Subjects and Study Design of Two Ongoing Clinical Trials in Patients With PNH

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OBJECTIVE

To demonstrate that suppression of mature CFD with OMS906 in a Phase 1 study provides scientific rationale for evaluating MASP-3 inhibition for the treatment of PNH

CONCLUSIONS

- In this Phase 1 study of healthy subjects, MASP-3 inhibitor OMS906 was well tolerated with no safety concerns
- OMS906 PK and PD profiles showed predictable systemic exposure, evidence of MASP-3 inhibition, and a long duration of action
- In PNH, targeting the alternative pathway via MASP-3 inhibition is predicted to block intravascular hemolysis and prevent extravascular hemolysis caused by C5 inhibitors
- Two ongoing open-label clinical trials are currently evaluating OMS906 in adults with PNH (EudraCT numbers: 2021-006930-37, 2022-002450-22)

AUTHOR DISCLOSURES

MG: Advisory board – Alexion (AstraZeneca Rare Disease), Novartis, Biocryst, Amgen, Sobi; honoraria/lecture fees – Sobi, Alexion (AstraZeneca Rare Disease), Novartis; consultancy – Regeneron, Biocryst. **WP, JH, EP**: Consultant – Omeros. **WJC**: Employee – Omeros.

BACKGROUND

- The alternative pathway of complement is implicated in a wide variety of diseases[1]
- CFD activates CFB, which drives the formation of AP C3 convertase and generates C3b. This process creates a positive feedback loop of protease complexes, which further activates downstream proteases (**Figure 1**)[1]
  - In PNH, unchecked AP activity leads to intravascular hemolysis; suppressing this lysis with terminal complement inhibition exacerbates AP-mediated extravascular hemolysis of PNH red blood cells via C3b opsonization[2]

Figure 1. Alternative Pathway Inhibition via MASP-3

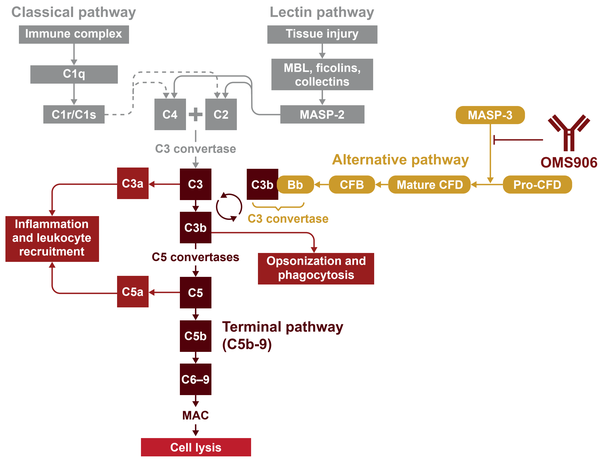


Figure adapted from Belcher *et al.* (2022).[4]

- MASP-3 is the activator of CFD and responsible for conversion of its zymogen form (pro-CFD) to mature CFD (**Figure 1**)[1]
- OMS906 is a humanized mAb that binds to the serine protease domain of MASP-3, thereby inhibiting its catalytic activity[3]
  - Preclinical data of OMS906 in mice and cynomolgus monkeys demonstrated the therapeutic potential of OMS906 to inhibit AP activity[3]
- As an upstream inhibitor, OMS906 is predicted to block intravascular hemolysis and, unlike C5 inhibitors, to prevent extravascular hemolysis in PNH[2]

METHODS

Trial Design

- This was a first-in-man, randomized, double-blind, single-center, placebo-controlled Phase 1 study of OMS906
- Subjects were randomized (6:2) into 9 escalating SAD cohorts (0.1–5 mg/kg IV and 3–8 mg/kg SC) receiving either OMS906 or placebo via infusion
- Eligible subjects for inclusion were healthy males or females aged 18–64 years at screening with a BMI of 20–32 kg/m^2 and weight of ≥50 kg

Trial Objectives

- The aim of this study was to assess the safety, tolerability, PK and PD of OMS906 in healthy subjects

RESULTS

Subject Demographics

- Overall, 72 subjects with a median age of 42 years (range, 20–63) and median BMI of 27.2 kg/m^2 (range, 21.0–31.4) were studied; 51.4% of subjects were female
- Demographics were generally balanced between the dosing cohorts and between the OMS906 versus placebo groups

Table 1. Pharmacokinetic Properties of OMS906 (PK Set)

Parameter	OMS906 IV Range Cohorts (n=30)	OMS906 SC Range Cohorts (n=22)
Serum concentration		
Geometric mean C_{max}, µg/mL	3.2–139.0	134.0–388.0
Geometric mean $AUC_{0\text{-}inf}$, h•mg/mL	0.3–53.2	8.1–38.8
Median T_{max}, h	0.7–2.5	96.0–239.4
Geometric mean $T_{½}$, h	94–399	239–406
Geometric mean clearance, mL/h		
CL	7.7–32.1	–
CL/F	–	14.1–28.3
Geometric mean volume of distribution, L		
V_{ss}	3.0–5.4	–
V_z	4.0–5.5	–
V_z/F	–	6.8–12.4

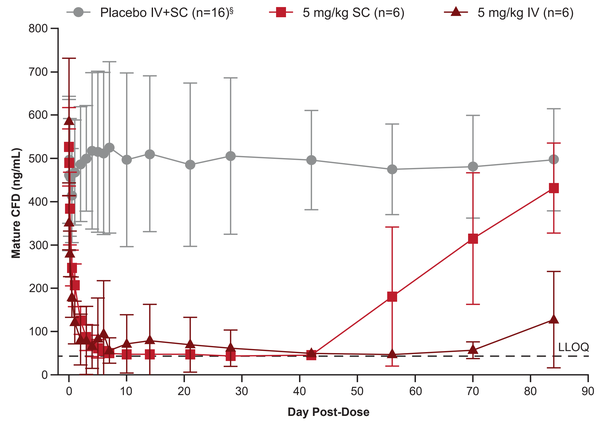
Pharmacokinetics

- OMS906 displayed consistent PK properties with dose proportionality (with non-linearity) for both IV and SC administration (**Table 1**)
  - A long half-life (geometric mean range 94–406 hours) was observed, with measurable drug concentrations detected at Day 85 for both IV (3 and 5 mg/kg) and SC (3, 5 and 8 mg/kg) OMS906 cohorts

Pharmacodynamics

- The key PD marker for MASP-3 inhibition—mature CFD—showed a dose-proportional response with rapid suppression and a substantial degree of suppression of long duration in subjects receiving 5 mg/kg OMS906 IV or SC versus placebo (**Figure 2**)

Figure 2. Mean (±SD) Mature CFD in Subjects Receiving 5 mg/kg IV and 5 mg/kg SC OMS906 Versus Placebo* Over Time†,‡



*Both IV and SC cohorts; †30 min post-dose to Day 85; ‡LLOQ was 43.9 ng/mL; values measured below this threshold were assigned LLOQ value; §Day 15 data shown for n=15 (1 subject data missing).

Safety

- OMS906 was well tolerated with most treatment-emergent adverse events (TEAEs) considered mild and short in duration (**Table 2**)
  - All TEAEs were transient and resolved without sequelae
  - There was one severe TEAE (tooth abscess) but no serious TEAEs, discontinuations due to AEs, or deaths
  - There were no reported hypersensitivity reactions
- Most TEAEs (58.8%) were determined not or unlikely related to OMS906
- The most frequent TEAEs were injection site reactions, which were reported in 27.8% of subjects and primarily seen with OMS906 SC infusion

Table 2. Treatment-Emergent Adverse Events (Safety Set)

	IV Cohorts (n=40)		SC Cohorts (n=32)		Overall (n=72)
	OMS906 (n=30)	Placebo (n=10)	OMS906 (n=24)	Placebo (n=8)	
TEAEs, n (%)	11 (36.7)	5 (50.0)	20 (83.3)	3 (37.5)	39 (54.2)
No. of events	18	14	42	11	85
Mild	8 (26.7)	4 (40.0)	18 (75.0)	2 (25.0)	32 (44.4)
Moderate	2 (6.7)	1 (10.0)	2 (8.3)	1 (12.5)	6 (8.3)
Severe	1 (3.3)	0	0	0	1 (1.4)
AE leading to study drug discontinuation	0	0	0	0	0
ISR, n (%)	1 (3.3)	0	17 (70.8)	2 (25.0)	20 (27.8)
No. of events	1	0	27	3	31
Bruising	1	0	3	0	4
Discomfort	0	0	0	1	1
Erythema	0	0	8	1	9
Induration	0	0	14	1	15
Warmth	0	0	1	0	1
Swelling	0	0	1	0	1

Presence of ADA

- The overall confirmed positive rate of ADAs was 14.8% in subjects receiving OMS906 (n=8/54)
  - There was no evidence of impact on PK or PD
- There were no incidences of hypersensitivity reactions or anaphylaxis

ONGOING EVALUATION OF OMS906 IN ADULTS WITH PNH

- Two ongoing open-label Phase 1b proof-of-concept clinical trials are currently evaluating safety, tolerability, PK, PD, and preliminary efficacy of OMS906 in adults with PNH
  - The first trial is enrolling patients with a sub-optimal response to ravulizumab treatment (**Table 3**)
  - The second trial is enrolling PNH patients who are complement inhibitor treatment naïve or have an inadequate response to C5 inhibitors (**Table 4**)

Table 3. Phase 1b Trial of OMS906 in PNH Patients with Sub-Optimal Response to Ravulizumab

Study ID	Intervention	Outcome Measures
OMS906-PNH-001 (Eudra CT number: 2021-006930-37)	Up to 6 doses of 3 mg/kg ***or*** 5 mg/kg IV OMS906 (8-week intervals; first in combination with ravulizumab, then as monotherapy)	***Primary:*** • To assess overall safety and tolerability ***Secondary:*** • To assess preliminary efficacy (increase of Hgb ≥2.0 g/dL from baseline) • To assess indicators of hemolysis (reticulocytes, LDH, number of blood transfusions) • To assess PK, PD, and ADAs

Table 4. Phase 1b Trial of OMS906 in PNH Patients who are Complement Inhibitor Treatment Naïve or Have an Inadequate C5 Inhibitor Response

Study ID	Intervention	Outcome Measures
OMS906-PNH-002 (Eudra CT number: 2022-002450-22)	Repeat dose of 5 mg/kg SC OMS906 (4-week intervals)	***Primary:*** • To assess overall safety and tolerability ***Secondary:*** • To assess preliminary efficacy by effect on hemolysis and anemia (Hgb and LDH levels, RBC transfusion burden) • To assess PK, PD, and ADAs

- Adults with a confirmed diagnosis of PNH by flow cytometry are eligible for inclusion provided they meet the following criteria:
  - **For OMS906-PNH-001**: Have a sub-optimal response to ravulizumab treatment (defined as Hgb level of <10.5 g/dL)
  - ***or***
  - **For OMS906-PNH-002**: Are complement inhibitor treatment naïve, or, alternatively, have an inadequate response to C5 inhibitors (eculizumab or ravulizumab), and Hgb level of <10.5 g/dL

ABBREVIATIONS

ADA, anti-drug antibody; AE, adverse event; AP, alternative pathway; AUC, area under the curve; BMI, body mass index; CFB, complement Factor B; CFD, complement Factor D; CL, clearance (IV administration); CL/F, apparent clearance (SC administration); C_{max}, maximum concentration; Hgb, hemoglobin; ISR, injection site reaction; IV, intravenous; LDH, lactate dehydrogenase; LLOQ, lower limit of quantification; mAb, monoclonal antibody; MAC, membrane attack complex; MASP, mannan-binding lectin-associated serine protease; MBL, mannan-binding lectin; PD, pharmacodynamics; PK, pharmacokinetics; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; SAD, single ascending dose; SC, subcutaneous; SD, standard deviation; TEAE, treatment-emergent adverse event; T_{max}, time to attain maximum observed concentration; $T_{½}$, terminal elimination half-life; V_{ss}, volume of distribution at steady state (IV administration); V_z, volume of distribution at terminal phase (IV administration); V_z/F, apparent volume of distribution at terminal phase (SC administration).

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DISCLAIMER

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

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