Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of the Alternative Pathway MASP-3 Inhibitor OMS906 in a Phase 1 Study of Healthy Subjects

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OBJECTIVE

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

CONCLUSIONS

- In this Phase 1 study of healthy subjects, MASP-3 inhibitor OMS906 was well tolerated with no safety concerns
- There were no serious AEs; the most common AEs were ISRs seen with SC infusion
- The observed PK and PD profiles were consistent with predictions from preclinical assessments, showing predictable systemic exposure, evidence of alternative pathway inhibition, and a long duration of action
- Further clinical study of OMS906 is warranted, including in patients with PNH (EudraCT number: 2021-006930-37)

BACKGROUND

- Dysregulation of the alternative pathway of complement is implicated in a wide variety of diseases, including PNH, C3G, aHUS, ANCA–associated vasculitis, and AMD[1]
- CFD drives formation of alternative pathway C3 convertase, generating C3b and creating a positive feedback loop of protease complexes (**Figure 1**), which can lead to inflammation, tissue destruction, and the intravascular and extravascular hemolysis observed in PNH[1]
  - 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 IgG4 mAb that binds to the serine protease domain of MASP-3, thereby inhibiting its catalytic activity[2]
  - Preclinical studies of OMS906 in mice and cynomolgus monkeys demonstrated inhibition of AP activity via MASP-3 inhibition[2]
  - The data indicate a therapeutic potential of OMS906 in the treatment of diseases associated with AP dysregulation, such as PNH

Figure 1. Alternative Pathway Inhibition via MASP-3

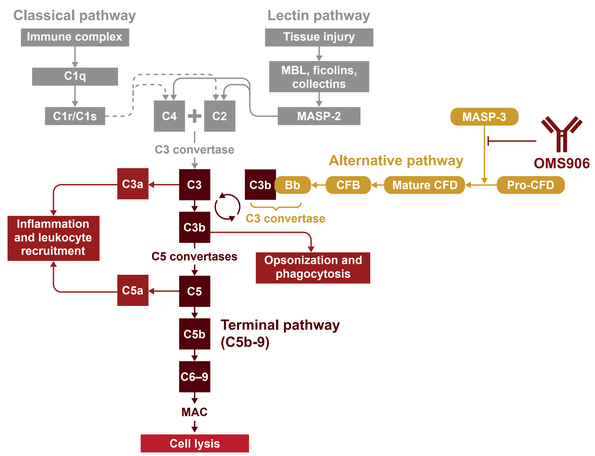


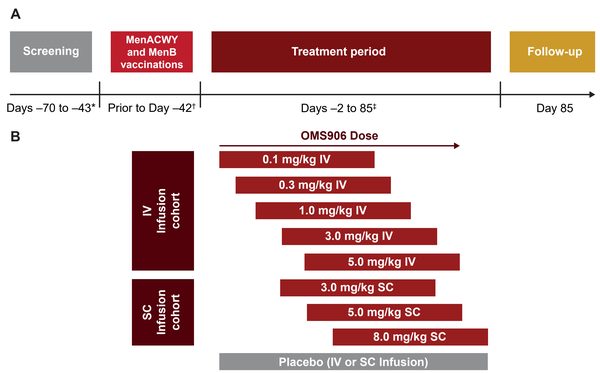
Figure adapted from Belcher *et al.* (2022).[3]

METHODS

Trial Design

- This was a randomized, double-blind, single-center, placebo-controlled Phase 1 study to evaluate safety, tolerability, PK, and PD of single-ascending IV and SC doses of OMS906 in healthy subjects (**Figure 2A**)
- Following screening, subjects received MenACWY and MenB vaccinations
- Subjects were randomized into escalating SAD cohorts that received 0.1 to 5.0 mg/kg IV and 3.0 to 8.0 mg/kg SC of either OMS906 or placebo via infusion (**Figure 2B**)

Figure 2. Trial Design



*Except 0.1 and 0.3 mg/kg IV cohorts (Day –28 and Day –3); †0.1 mg/kg and 0.3 mg/kg IV cohorts did not receive MenACWY and MenB vaccinations; ‡Clinic from Day –2 (admission) to ~168 hours after study drug administration. Final safety assessments and clinical sampling were performed during the last confinement visit on Days 84–85.

Study Subjects

- Eligible subjects for inclusion in this trial 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
  - Subjects of child-bearing potential took the appropriate precautions

Trial Objectives and Endpoints

- The primary and secondary trial objectives and endpoints are listed in **Table 1**

Statistical Analysis

- For this study, no prospective calculations of statistical power were made. The sample size was selected to provide information on safety, tolerability, PK, and PD following single dosing of OMS906

Table 1. Trial Objectives and Endpoints

	Objectives	Endpoints
Primary	To assess safety and tolerability of OMS906 in healthy human subjects	• Adverse events
Secondary	• To characterize the PK and PD of single-ascending IV and SC doses of OMS906 • To assess the presence of ADAs against OMS906 in healthy subjects	• Serum OMS906 concentrations • Serum PK parameters (C_{max}, T_{max}, $T_{½}$, $AUC_{0\text{-}inf}$, CL, CL/F, V_z, V_{ss}, V_z/F) • Change from baseline in mature CFD plasma concentrations • Incidence of ADAs in serum

RESULTS

Subject Demographics

- Overall, 72 subjects were enrolled, and demographics (**Table 2**) were generally balanced between the dosing cohorts (data not shown), and between the OMS906 versus placebo groups (data not shown)

Table 2. Subject Demographics (Safety Set)

Parameter	Overall (n=72)
Median age, years (range)	42 (20–63)
Median BMI, kg/m^2 (range)	27.2 (21.0–31.4)
Median weight, kg (range)	77.0 (50.8–105.7)
Sex, n (%)	
Female	37 (51.4)
Male	35 (48.6)
Race, n (%)	
White	40 (55.6)
Black or African American	22 (30.6)
Asian	3 (4.2)
American Indian or Alaska Native	2 (2.8)
Multiple	5 (6.9)
Ethnicity, n (%)	
Hispanic or Latino	4 (5.6)
Not Hispanic or Latino	68 (94.4)

Pharmacokinetics

- OMS906 displayed consistent PK properties with dose proportionality (with non-linearity) for both IV and SC administration (**Table 3**)
  - 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

Table 3. 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

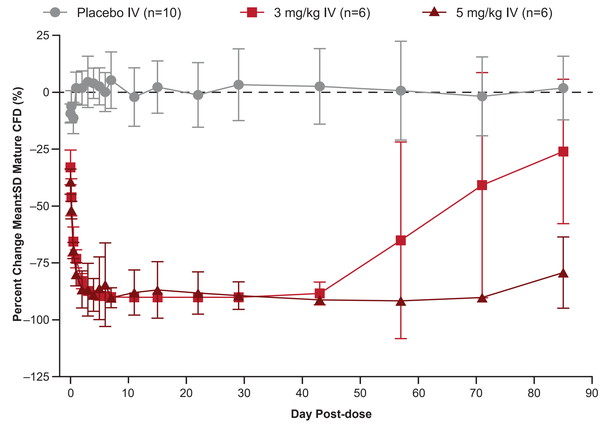
Pharmacodynamics

- 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 3 and 5 mg/kg OMS906 IV versus placebo (**Figure 3**)

Safety

- OMS906 was well tolerated with most treatment-emergent adverse events (TEAEs) considered mild and short in duration (**Table 4**)
  - All TEAEs were transient and resolved without sequelae
  - There were no serious TEAEs, discontinuations due to AEs, or deaths
  - There were no reported hypersensitivity reactions
- Most TEAEs (58.8%) were determined unlikely to be due to OMS906 with the exception of ISRs, which were the most frequently reported TEAE in 27.8% of subjects

Figure 3. Percent Change of Mean (±SD) Mature CFD in Subjects Receiving 3 mg/kg IV and 5 mg/kg IV OMS906 Versus Placebo Over Time*,†



*30 min post-dose to Day 85; †BLQ was 43.9 ng/mL; values measured below this threshold were assigned BLQ value.

Table 4. 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)
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
AE leading to study drug discontinuation	0	0	0	0	0

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

Study Limitations

- While this study demonstrated that OMS906 suppressed mature CFD production in healthy subjects, OMS906 requires further evaluation in a disease population, such as PNH

ABBREVIATIONS

ADA, anti-drug antibody; aHUS, atypical hemolytic uremic syndrome; AMD, age-related macular degeneration; ANCA, anti-neutrophil cytoplasmic autoantibody; AP, alternative pathway; AUC, area under the curve; BLQ, below limit of quantification; BMI, body mass index; C3G, complement 3 glomerulopathy; CFB, complement factor B; CFD, complement factor D; CL, clearance (IV administration); CL/F, apparent clearance (SC administration); C_{max}, maximum concentration; COVID-19, coronavirus disease 2019; ISR, injection site reaction; IV, intravenous; mAb, monoclonal antibody; MAC, membrane attack complex; MASP, mannan-binding lectin-associated serine protease; MBL, mannan-binding lectin; Men, meningococcal; MenACWY, *Neisseria meningitidis* serotypes A, C, W135 and Y vaccine; MenB, *Neisseria meningitidis* serotype B vaccine; PD, pharmacodynamics; PK, pharmacokinetics; PNH, paroxysmal nocturnal hemoglobinuria; 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).

REFERENCES

1. Barratt J, Weitz I. *Front Immunol* 2021;12:712572.
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DISCLAIMER

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

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