Population Pharmacokinetic/ Pharmacodynamics and Clinical Pharmacology of Zaltenibart (OMS906) in Healthy Subjects and Patients with PNH

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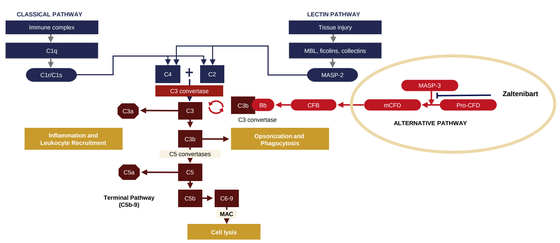
BACKGROUND

- Mannan-binding lectin-associated serine protease-3 (MASP-3), the most upstream activator of the alternative pathway (AP) of complement, cleaves pro-complement factor D (CFD) into mature CFD (mCFD), a rate limiting step in the AP[1,2] (**Figure 1**)
- MASP-3 is being investigated as a novel therapeutic target for a variety of AP-mediated diseases, including paroxysmal nocturnal hemoglobinuria (PNH), a rare and life-threatening disorder involving complement dysregulation[1]
- Zaltenibart (OMS906), a highly selective humanized IgG4 mAb, binds to and inhibits MASP-3, blocking CFD maturation and inhibiting downstream AP activity[3,4]
- Pharmacokinetic (PK) and pharmacodynamic (PD) profiles of zaltenibart have been evaluated in healthy subjects[4,5] and in patients with PNH[6,7]
- The clinical efficacy of zaltenibart has been reported in PNH patients naïve to C5 therapy (OMS906-PNH-002) as well as those with suboptimal response to C5 therapy (OMS906-PNH-001),[8-10] with dose response observed in patients in the latter
- Here we report on PK/PD exposure-response relationships for zaltenibart on PD and clinical efficacy measures

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



OBJECTIVE

- To describe the PK/PD relationships and exposure-response modeling for zaltenibart on biomarker measures (free MASP-3, mCFD), AP activity, and clinical efficacy measures (lactate dehydrogenase [LDH], hemoglobin [Hgb], absolute reticulocyte count [ARC]) to inform the optimal dosing regimen for patients with PNH

METHODS

Data sources:

- PK data from 2 Phase 1 trials in healthy subjects (OMS906-NHV-002 and OMS906-NHV-004)[4,5]
- PK, PD, and clinical data from studies in patients with PNH (OMS906-PNH-001 and OMS906-PNH-002)[4,5,9,10]

Healthy subject assessments:

- Blood samples from healthy subjects exposed to zaltenibart were analyzed for free MASP-3, AP activity, and zaltenibart in serum and mCFD in plasma
- The impact of zaltenibart on downstream AP activity was evaluated using a rabbit red blood cell (RBC) lysis assay in serum samples

PNH patient population PK/PD modeling:

- Sparse sampling PK and PD measures were collected from patients and a series of exposure-response models assessed the relationship between zaltenibart exposure and:
  - (i) PD biomarkers (free MASP-3, mCFD, and AP activity), and
  - (ii) Clinical efficacy (LDH, Hgb, ARC)
- The impact of covariates (age, weight, gender, baseline LDH/Hgb/mCFD/free MASP-3 and history of aplastic anemia [AA] or myelodysplastic syndrome [MDS]) was also explored

RESULTS

Results: PK Parameters

- A dose range of up to 8 mg/kg IV as a single dose has been explored in Phase 1 studies in healthy subjects
- Zaltenibart C_{max} increased in a dose-proportional manner and exposure (AUC) increased in a roughly proportional manner over single doses in the range of 1-8 mg/kg IV (**Figure 2, Table 1**)
  - Target Mediated Drug Disposition was apparent at lower concentrations/doses
- PK parameters observed include:
  - $T_{1/2}$: ~17 days
  - CV%: 13-14

Figure 2. PK Parameters of Zaltenibart in Healthy Subjects (Single-Dose Range 1-8 mg/kg)

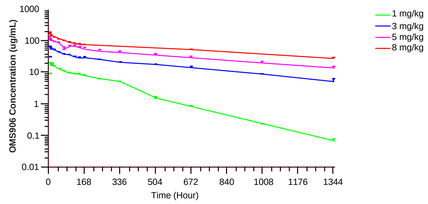


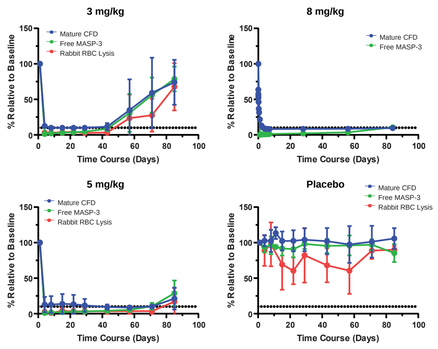
Table 1. Dose-proportional AUC_{1344} and C_{max} in Healthy Subjects After Zaltenibart Exposure

Parameter	Slope	Lower_90CI	Upper_90CI
AUC_{1344}	1.2215	1.0584	1.3846
C_{MAX}	0.9722	0.7937	1.1508

Results: Biomarkers (Free MASP-3, mCFD) and AP Activity

- Administration of zaltenibart resulted in a rapid and sustained dose-dependent decrease in free MASP-3, mCFD, and AP activity at doses ranging from 1-8 mg/kg IV (**Figure 3**)
  - This change was not observed in placebo exposed subjects

Figure 3. Dose-dependent and Concordant Suppression of Free MASP-3, mCFD, and AP Function Following Zaltenibart Exposure



*Rabbit RBC lysis data was not yet available for the 8 mg/kg group.

Results: Inhibition of Free MASP-3 and the AP in Healthy Subjects

- Zaltenibart administration in healthy subjects at 1 mg/kg IV and higher was associated with near-complete maximum inhibition of biomarker free MASP-3 and markedly reduced AP activity (**Figure 4**)
- Derived EC_{98} values from these assays are used to determine the minimal (i.e., threshold) concentration required for control of hemolysis: set at 18000 ng/mL (18 µg/mL) (**Table 2**)

Figure 4. Inhibition of Free MASP-3 and AP Activity vs. Zaltenibart Concentration

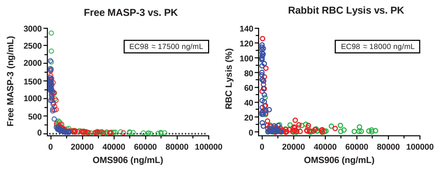


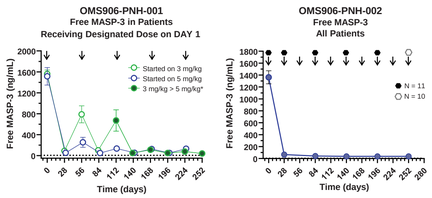
Table 2. EC_x Estimates Across Biomarker and AP Function Parameters

Measure	EC_{50}	EC_{98}	R^2
Free MASP-3 (ng/mL)	2107	17508	0.9115
Rabbit RBC Lysis (% activity)	1511	17994	0.8016

Results: Inhibition of Free MASP-3 in Patients with PNH

- Zaltenibart has been assessed as a treatment option for patients with PNH with suboptimal response to C5 therapy (OMS906-PNH-001) as well as for those who were naïve to C5 therapy (OMS906-PNH-002)
- In OMS906-PNH-001, adjunctive treatment with zaltenibart reduced free MASP-3 levels in patients, and this reduction was better sustained at the 5 mg/kg IV dose vs 3 mg/kg IV (**Figure 5**)
- In OMS906-PNH-002, monotherapy with zaltenibart 5 mg/kg SC (comparable exposure to 3 mg/kg IV) also showed sustained, reduced free MASP-3 levels (**Figure 5**)

Figure 5. Mean (±SE) Free MASP-3 Concentrations vs. Time by Initial Dose



*Indicates the interval in which 6 of 7 patients switched from 3 mg/kg IV to 5 mg/kg IV.

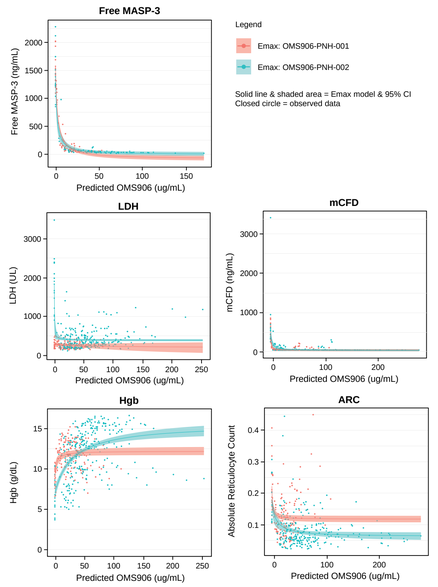
Results: Clinical Efficacy and Dose Response Observed in PNH Patients Correlates with Biomarker Measures

- Clinical efficacy, with improvements in Hgb and reductions in ARC, was observed in patients in study OMS906-PNH-001 in a dose-dependent manner
  - Greater magnitude and duration of effects were observed at the highest dose (5 mg/kg IV Q8W vs. 3 mg/kg IV Q8W)
  - Some patients did not demonstrate sufficient control of EVH at the 5 mg/kg IV dose, suggesting a need to escalate to a higher dose
- The improved clinical efficacy in hematological markers (i.e., Hgb and ARC) at the 5 mg/kg IV dose compared to the 3 mg/kg IV dose in patients with PNH was associated with more consistent (less saw tooth pattern) and durable reductions in free MASP-3 levels

Results: Zaltenibart Exposure-Response Modeling in Patients

- Patient-level data demonstrate that zaltenibart improves key biomarker (free MASP-3 and mCFD) and hematological markers (Hgb, ARC, and LDH) in an exposure-related manner (**Figure 6**)

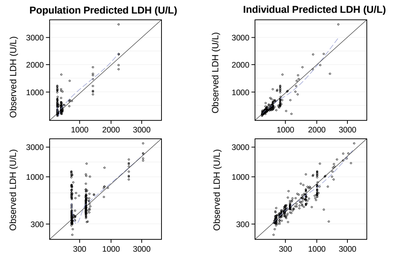
Figure 6. Exploratory E_{max} Model PK/PD Plots for PD Biomarker (Free MASP-3, mCFD) and Clinical Efficacy Measures (Hgb, ARC, LDH)



Results: Zaltenibart Population PK/PD Modeling

- Populations were modeled separately to minimize study-level bias, accounting for different baseline values and potential differential responses between the two patient populations (OMS906-PNH-001 and OMS906-PNH-002)
- Overall, population and individual predicted values for free MASP-3, mCFD, LDH, ARC and Hgb correlated well with observed values for both population and individual estimates, thus enabling the subsequent exposure-response modeling to be adequately predictive of clinical and biomarker responses
  - An illustrative example for LDH from the OMS906-PNH-002 study is shown in **Figure 7**

Figure 7. Observed vs. Predicted Values for LDH from OMS906-PNH-002

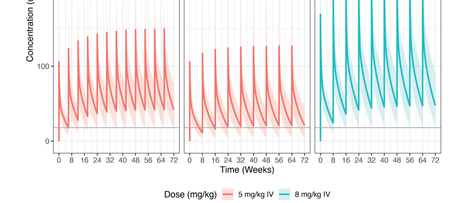


- For OMS906-PNH-001:
  - For free MASP-3, history of AA/MDS was a significant covariate for IC_{50}
  - No covariates were found that impacted any of the other models (i.e., mCFD, LDH, ARC or Hgb)
- For OMS906-PNH-002:
  - The addition of gender to the LDH model was significant (males had higher baseline values)
  - For Hgb, gender on the Hill parameter and history of AA/MDS on EC_{50} were found to be significant covariates
  - For free MASP-3, baseline levels were a significant covariate for IC_{50}
  - For both mCFD and ARC, no significant covariates were identified
- For both studies, and all parameters studied, indirect exposure-response (sigmoid E_{max}) models described the data well and accounted for any hysteresis

Results: Zaltenibart Dose/Dosing Regimen Simulations

- Based on the mechanism of action of zaltenibart and the high degree of concordance observed between zaltenibart concentrations and clinical and biomarker parameters and exposure-response models, a minimal (threshold) concentration of 18000 ng/mL (18 µg/mL), has been identified, which equates to an EC_{98} for free MASP-3
- Using this threshold concentration, dose/dosing regimen simulations demonstrate that 8 mg/kg IV Q8W generates sufficient exposures to exceed the minimal threshold for the majority of patients after the first dose across the dosing interval, and particularly at steady state (**Figure 8**)

Figure 8. Dose and Dose Regimen Simulations



SUMMARY AND CONCLUSIONS

- PK/PD and clinical data from our studies demonstrate that zaltenibart reduces the production of mCFD through inhibition of MASP-3, with a concordant reduction in free MASP-3 levels and resulting inhibition of AP activity
- Free MASP-3 appears to be a particularly sensitive and useful marker for setting the minimal (i.e., threshold) concentration needed for effect
- Clinical data from Phase 1 and 2 trials demonstrate that zaltenibart improves key hematological markers (Hgb, ARC, and LDH) in patients with PNH in a dose- and exposure-related manner
- Dose/dose regimen simulations demonstrate that a dose of 8 mg/kg Q8W is optimal for providing not only adequate response in hematologic markers, but also for durability of response in controlling hemolysis in patients with PNH
- Zaltenibart monotherapy in patients with PNH with dosing at 8 mg/kg Q8W is being evaluated in Phase 3 clinical trials

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DISCLAIMER

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

ABBREVIATIONS

AP, alternative pathway; BTH, breakthrough hemolysis; CFB, complement factor B; CFD, complement factor D; IgG4, immunoglobulin G4; IV, intravenous; mAb, monoclonal antibody; 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; SC, subcutaneous.

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