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P787 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

Topic: 12. Bone marrow failure syndromes incl. PNH - Clinical

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Background:

The alternative pathway (AP) of complement is implicated in a wide variety of diseases. Complement Factor D (CFD) drives formation of AP C3 convertase, generating C3b and activating downstream proteases. In paroxysmal nocturnal hemoglobinuria (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.

Mannan-binding lectin-associated serine protease-3 (MASP-3) is the activator of CFD. OMS906 is a humanized monoclonal antibody that binds to and inhibits MASP-3. Preclinical data demonstrate the therapeutic potential of OMS906 to inhibit AP activity. As an upstream inhibitor, OMS906 is predicted to block intravascular hemolysis and, unlike C5 inhibitors, to prevent extravascular hemolysis in PNH.

Aims:

We report the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of OMS906 in healthy subjects. We also present the study design of two ongoing clinical trials of OMS906 in patients with PNH.

Methods:

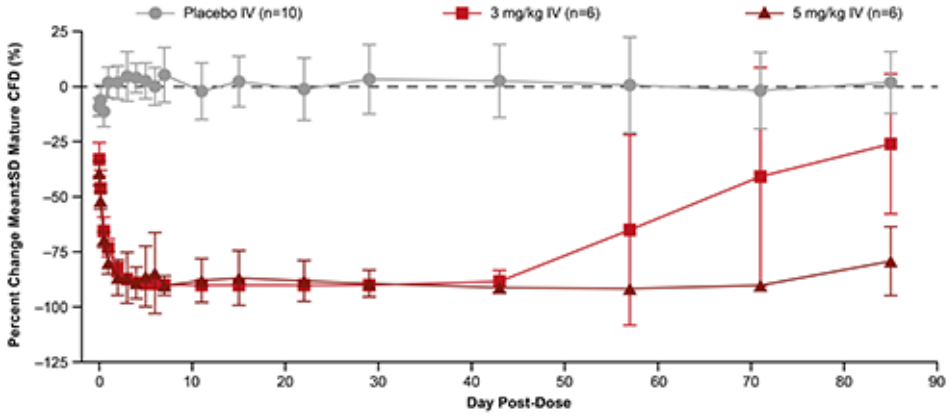
This randomized, double-blind, single-center, placebo-controlled Phase 1 study of OMS906 enrolled healthy adults. Subjects were randomized (6:2) into nine single-ascending dose cohorts (0.1–5 mg/kg intravenous [IV]; 3–8 mg/kg subcutaneous [SC]) receiving either OMS906 or placebo via infusion. The primary objective was safety and tolerability. Secondary objectives included PK and PD of OMS906, and presence of anti-drug antibodies (ADAs).

Results:

Overall, 72 subjects were studied; 54 received OMS906 (30 IV; 24 SC). Median age was 42 years (range, 20–63); 51.4% were female. OMS906 displayed consistent PK properties with dose proportionality. Median T_{max} was 0.7–2.5 h (IV) and 96–239 h (SC). A long half-life (geometric mean range, 94–406 h) was observed, with measurable drug concentrations at Day 85 for higher doses. The key PD marker for MASP-3 inhibition—mature CFD—showed a dose-proportional response with rapid suppression and long duration in subjects receiving 3 and 5 mg/kg OMS906 IV versus placebo (**Figure**).

OMS906 was well tolerated. Most treatment-emergent adverse events (TEAEs) were mild (44.4% of subjects) and short in duration. There was one severe TEAE (tooth abscess) but no serious AEs, discontinuations due to AEs, or deaths. Most TEAEs (58.8%) were determined not or unlikely related to OMS906. The most frequent TEAEs were injection site reactions (27.8% of subjects) primarily seen with OMS906 SC infusion. The confirmed positive ADA rate was 14.8% (n=8/54) in subjects receiving OMS906. There were no hypersensitivity reactions.

Figure. Percent Change of Mean (±SD) Mature CFD in Subjects Receiving 3 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.
BLQ, below limit of quantification; CFD, complement Factor D; IV, intravenous; SD, standard deviation.

Two ongoing open-label, multi-center clinical trials are evaluating safety, tolerability, PK, and PD of OMS906 in adults with PNH. The first is enrolling patients with a sub-optimal response to ravulizumab treatment; the second is enrolling treatment-naïve PNH patients. Endpoints indicating cessation of hemolysis in PNH include increased hemoglobin, change in lactate dehydrogenase and reticulocyte counts, and reduction in blood transfusion requirements.

Summary/Conclusion:

In a Phase 1 study, MASP-3 inhibitor OMS906 was well tolerated with no safety concerns. PK and PD profiles showed predictable systemic exposure, evidence of MASP-3 inhibition, and a long duration of action.

OMS906 demonstrated inhibition of mature CFD production in healthy subjects, and further study is warranted in a patient population. In PNH, targeting the AP via MASP-3 inhibition is predicted to block intravascular hemolysis and prevent extravascular hemolysis caused by C5 inhibitors.