Modeling and Simulation of Eculizumab in Paroxysmal Nocturnal Hemoglobinuria (PNH) and Atypical Hemolytic Uremic Syndrome (aHUS) Patients: Learning from One Indication to the Next

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INTRODUCTION

- Eculizumab (h5G1.1-mAb) is a humanized monoclonal antibody (mAb) that was derived from the murine anti-human C5 antibody m5G1.1 that specifically binds the terminal complement protein C5, thereby inhibiting its cleavage to C5a and C5b during complement activation.
- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, debilitating and life-threatening genetic disorder of hemopoietic stem cells characterized by chronic complement-mediated intravascular hemolysis that frequently leads to debilitating clinical symptoms and life-threatening complications such as thromboembolism (TE). Eculizumab concentrations greater than 35 µg/mL was set as the lower limit of target concentration range to achieve reduction in intravascular hemolysis in majority of PNH patients.
- Atypical hemolytic-uremic syndrome (aHUS) is a rare, progressive, serious and life-threatening disorder characterized by chronic uncontrolled complement activation leading to microangiopathic hemolytic anemia, thrombocytopenia, and organ damage, including renal failure.

OBJECTIVE

The goal of this project was to leverage a population PK model previously constructed in patients with PNH and develop optimal dosing strategies in patients with aHUS, a systemic life-threatening, rare genetic disease that involves uncontrolled and excessive activation of complement, leading to thrombotic microangiopathy (TMA), predominantly in the kidneys, but also affecting other vital organs.

As local eculizumab concentration in vital organs may be lower than that circulating in serum, 50 µg/mL was chosen as the lower limit of target concentration range.

METHODS

- Serum concentrations of eculizumab were assayed using a validated ELISA assay.
- Population PK analysis of eculizumab was performed in patients with PNH using a one-compartment model. Population PK modeling was performed using NONMEM (Version VI Level 1.2 or higher) (Globomax, Hanover, MD). The first-order conditional estimation ("FOCE") with the INTERACTION option was used when possible (assuming that convergence can be reached within a reasonable timeframe).
- The population PK model of eculizumab was coded in Trial Simulator® (V2.2.1) and simulations were performed to optimize dosing in adult, adolescent and pediatric patients with aHUS.

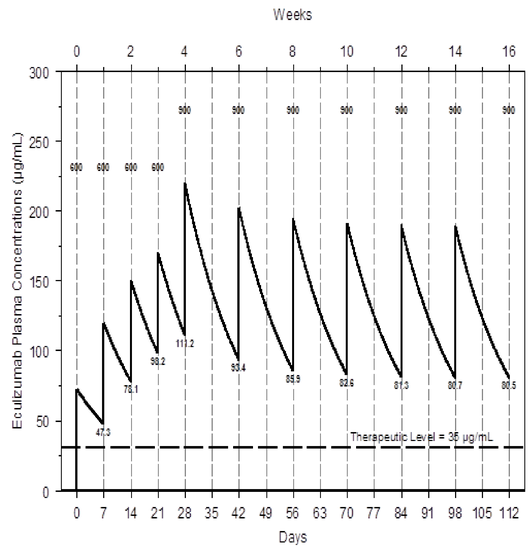
RESULTS – Adult Patients with PNH

Population PK Modeling of Eculizumab in Patients with PNH

- Population PK analysis of eculizumab was performed based on data collected in a total of 177 patients with PNH.
- The overall population included 29 Japanese and 148 Western patients with PNH.
- The following dosing regimen was used in all studies in adult patients with PNH:

For Patients 18 Years and Older	
Induction Phase	**Maintenance Phase**
600 mg Weekly for 4 Weeks	900 mg at Week 5 then Every 2 Weeks

- A one-compartment PK model provided an adequate quality-of-fit of peak and trough concentrations of eculizumab to achieve a complete and sustained functional complement inhibition.
- An example of predicted concentration-time profile of eculizumab in a typical 75-kg patient with PNH is presented below.
- In patients with PNH, uncontrolled complement activation occurs in red blood cell, platelets etc. and eculizumab concentrations greater than 35 µg/mL provided reduction in intravascular hemolysis in majority of patients with PNH.
- The maximum concentration measured in one of the PNH studies was 700 µg/mL and was safely tolerated by patients with PNH and hence considered to be the upper limit of target concentration.



- The CL of eculizumab in male and female patients were 0.0226 and 0.0193 L/h, respectively. The differences in CL between male and female patients were not deemed clinically relevant.
- In 2007, eculizumab was approved for treatment of PNH based on evidence of effectiveness from clinical studies; study results demonstrated that eculizumab induces a significant reduction in hemolysis and TE events as well as improvements in clinical symptoms, quality of life, and fatigue, with sustained response and long-term safety in patients with PNH.
- A small proportion of patients with PNH experienced a trough eculizumab concentration of <35 µg/mL as well as breakthrough hemolysis through maintenance phase of treatment. This breakthrough was generally associated with a rise in LDH and return of worsening of symptoms and other associated risks of hemolysis.

RESULTS – Adult and Pediatric Patients with aHUS

Learning from One Indication to the Next: Simulations of Eculizumab to Support Dosing Rationale in Adult and Pediatric Patients with aHUS

- The wide range of body weights in PNH patient population (43.5 to 120.5 kg) was used to assess the effect of body weight on PK parameters for eculizumab and refine predictions in aHUS patients with very low body weights (i.e., neonates and infants) by integrating an allometric scaling component into the population PK model.
- Simulations were performed to determine dosing in adult, adolescent and pediatric patients with aHUS resulting in a complete and sustained terminal complement inhibition.
- Data from previous PNH studies have shown that eculizumab concentrations greater than 35 µg/mL provided reduction in intravascular hemolysis in majority of patients with PNH. In order to maximize the clinical benefit in patients with aHUS, trough serum levels greater than 50 µg/mL were targeted given the possibility that the local eculizumab concentration in non-well-perfused areas of vital organs such as kidney, CNS, brain etc. may be lower than that measured and circulating in serum. The upper limit of target concentration of 700 µg/mL was safely tolerated in previous studies.
- Based on trial simulations performed using models based on PNH clinical PK data, the following induction and maintenance dosing schemes were predicted to result in eculizumab concentrations within the targeted range (50 – 700 µg/mL).

For Patients 18 Years and Older	
Induction Phase	**Maintenance Phase**
900 mg Weekly for 4 Weeks	1200 mg at Week 5 then Every 2 Weeks

For Patients less than 18 Years of Age		
Weight Group	**Induction Phase**	**Maintenance Phase**
≥ 40 kg	900 mg Weekly for 4 Weeks	1200 mg at Week 5 then Every 2 Weeks
30 - <40 kg	600 mg Weekly for 2 Weeks	900 mg at Week 3 then Every 2 Weeks
20 - <30 kg	600 mg Weekly for 2 Weeks	600 mg at Week 3 then Every 2 Weeks
10 - <20 kg	600 mg Weekly for 1 Week	300 mg at Week 2 then Every 2 Weeks
5 - <10 kg	300 mg Weekly for 1 Week	300 mg at Week 2 then Every 3 Weeks

Population PK Modeling to Confirm Final Dosing Rationale in Adult and Pediatric Patients with aHUS

- The following two prospective studies were conducted using the proposed dosing regimen:
  - **Study C08-002A/B:** A Phase 2 Study for evaluation of safety and efficacy of eculizumab in adolescent and adult patients with aHUS and clinical evidence of progressing TMA (Treated 16 adults; 1 adolescent patients)
  - **Study C08-003A/B:** A Phase 2 Study for evaluation of safety and efficacy of eculizumab in adolescent and adult patients with aHUS who had longer duration of disease, chronic kidney damage and prolonged treatment with Plasma exchange or infusion (Treated 15 adults; 5 adolescent patients)
- In addition, the following retrospective data was collected:
  - **Study C09-001r:** A Retrospective, Observational Study evaluating the safety and efficacy of eculizumab in pediatric, adolescent and adult patients (Data collected on 30 Pediatric and Adult patients; 20 of 30 patients provided samples for PK-PD analysis). Dosing regimen in this study was implemented by the treating physician.
- Data from 57 patients with aHUS from the above 3 studies showed that eculizumab concentrations were all within the target concentration range (50 – 700 µg/mL), with the exception of 1 patient in the Induction and 4 patients in the Maintenance Phase for a transient period of time. Observed data show that trough concentrations of greater than 50 µg/mL resulted in functional complement inhibition (PD parameter % hemolysis) in all patients with aHUS.
- In addition free C5 is deemed to be an important parameter to ensure complete/sustained terminal complement inhibition for patients with aHUS. Additional PK/PD modeling of free C5 is discussed in Abstract #387 suggest that effective concentration of 50 to 150 µg/mL for an optimal inhibition of C5.
- Dosing regimens for pediatric, adolescent and adult patients recommended and treated in protocols C08-002A/B and C08-003A/B were approved in 2011 for treatment in patients with aHUS.
- Overall, the dosing strategy as specified in USPI and SmPC generally resulted in eculizumab exposure within the target concentration range (50-700 µg/mL). In turn, this was linked to efficacy in aHUS patients.

CONCLUSION

- The PK of eculizumab in patients with PNH was successfully leveraged to optimize dosing strategy in patients with aHUS.
- This dosing recommendation resulted in drug exposures in pediatric and adult patients with aHUS within the targeted range of 50-700 µg/mL. Based on observed safety and efficacy, in 2011, eculizumab (Soliris®) was approved for the treatment of aHUS.
- The PK knowledge in PNH and aHUS patients is being further leveraged to optimize dosing in other complement-mediated rare diseases.

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