Population Pharmacodynamic/Pharmacokinetic Modeling of Eculizumab and Free Complement Component Protein C5 in Pediatric and Adult Patients with Atypical Hemolytic Uremic Syndrome (aHUS)

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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.
- 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. A target concentration range of 50 to 700 µg/mL was selected in order to maximize the clinical benefit.
- In 2011, eculizumab (Soliris®) was approved for the treatment of aHUS was based on data from two prospective studies (Studies C08-002A/B and C08-003A/B) and one retrospective study C09-001r.

OBJECTIVE

- The goal of this project was to develop a population pharmacokinetic/pharmacodynamic (PK/PD) model to establish the relationship between serum concentrations of eculizumab and free C5 concentrations in patients with aHUS.

METHODS

- Serum concentrations of eculizumab were assayed using a validated ELISA assay, PD (% hemolysis) using a validated hemolysis assay and free C5 using a validated electrochemiluminescence immunoassay.
- Data from the following two prospective studies were used:
  - **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, data from the following retrospective study was used:
  - **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.

METHODS

Dosing Regimen as per USPI and SmPC

- The following dosing regimen was proposed based on trial simulations and subsequently approved in 2011.

For Patients 18 Years of Age 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/PD modeling of eculizumab was first performed using data collected in prospective studies (C08-002A/B and C08-003A/B). In a second step, PK/PD modeling was performed by including data from the 20 patients (of 30) in the retrospective study (C09-001r) that had samples for analyses.
- Population PK/PD modeling was performed using NONMEM (Version VI). The first-order conditional estimation ("FOCE") with the INTERACTION option was used.

Population PK Modeling of Eculizumab

- A one-compartment PK model provided an adequate quality of fit of peak and trough concentrations of eculizumab.
- PK parameters of eculizumab from the prospective and retrospective studies were similar since "study effect" on CL and V_c were found to be not significant at the 5% level (P>0.05)
- Typical CL and Vc of eculizumab in patients with aHUS were 14.6 mL/h and 6.14 L, respectively.

Population PK /PD Modeling of Free Complement Component Protein C5

- Relationship between serum concentrations of eculizumab and free C5 was modeled using an inhibitory E_{max} model.

$$C5 = E_0\left(1 - I_{max}\left(\frac{C_{ecu}{}^H}{IC_{50}{}^H + C_{ecu}{}^H}\right)\right)$$

- Where E_0 is the baseline, I_{max} is the maximum inhibition, C_{ecu} is the concentration of eculizumab, IC_{50} is the concentration associated to 50% of the maximum effect, and H is the Hill factor.

Population PK /PD Modeling of Hemolytic Activity

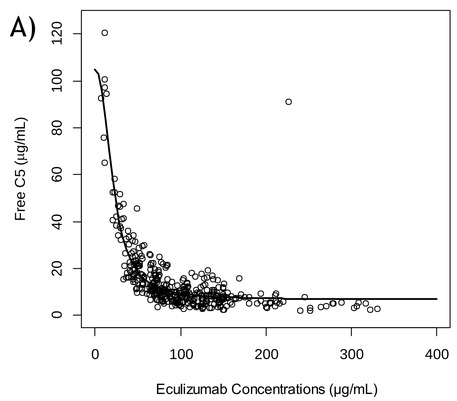
- In addition, PK/PD modeling of hemolytic activity was performed using the following cumulative Weibull function.

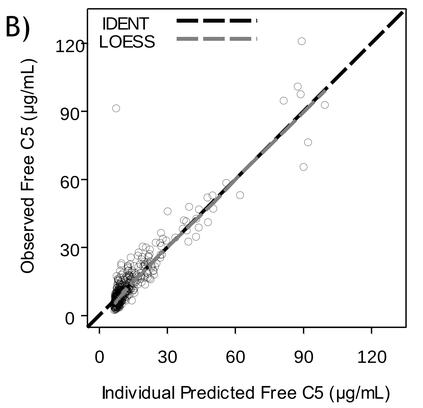
$$\text{Hemolysis}(\%) = E_0 - \left(E_{diff} \times \left(1 - e^{-\left(\frac{C_{ecu}}{C_{deff}}\right)^{Sf}}\right)\right)$$

- Where C_{ecu} is the observed concentration, E_{diff} is the difference between the effective concentrations to provide 100% of the maximum effect (E_{max}) and the baseline values (E_0), C_{deff} is the effective concentrations (analogous to E_{50} in a regular E_{max} model) to provide 1/e (36.8%) of the effect (C_{deff}) relative to E_0, and Sf determines the steepness of the PK/PD relationship.

RESULTS – Free C5 and Percent Hemolysis

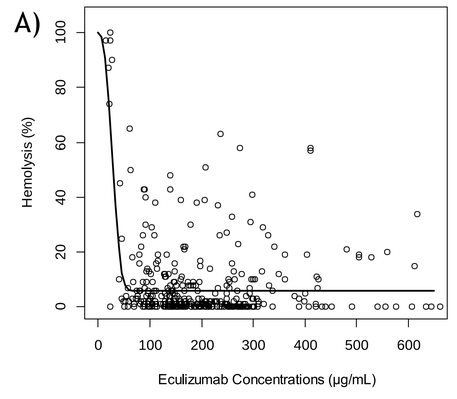
The PK/PD relationship of free C5 and goodness-of-fit derived with the final PK/PD model are presented below (Pane A and B, respectively)

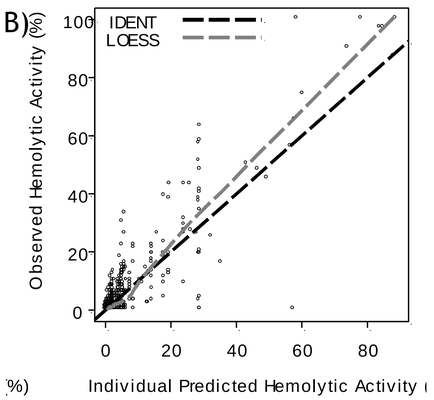




- A steep concentration-effect relationship was observed for the reduction of free C5. Effective eculizumab concentration for an optimal inhibition of C5 ranged between 50 and 150 µg/mL (Panel A) .
- The PK/PD for C5 model resulted in a good quality of fit (Panel B)
- Based on the final PK/PD model for free C5:
  - The maximum percent inhibition (I_{max}) of eculizumab on free C5 was 93.5%.
  - Eculizumab concentrations of 50, 100 and 150 µg/mL would be expected to result in 81.5%, 90.6% and 92.1% inhibition of free C5.

The PK/PD relationship of % hemolysis in the PD hemolytic assay and goodness-of-fit derived with the final PK/PD model are presented below (Panel A and B, respectively)





- A very steep concentration-effect relationship on PD percentage hemolysis was observed.
- A full inhibition of PD hemolytic activity was observed in prospective studies C08-002A/B and C08-003A/B.
- A total of 13 (22%) patients from retrospective Study C09-001r had PD hemolysis values >20% after eculizumab treatment. It is to be noted that some of these patients did not receive eculizumab dosing regimen stated in the USPI.

- Based on the PK/PD model, eculizumab concentrations of 50, 100 and 150 µg/mL would be expected to result in 81.5%, 90.6% and 92.1% suppression of hemolysis.
- PD hemolytic assay results should be interpreted with caution since (1) hemolysis of red blood cells (RBC) is not the primary pathophysiology of aHUS and (2) the variability in the bioanalytical assay must be considered.

CONCLUSION

- Based on the observed efficacy and safety profile, dosing regimens for adult and adolescent patients recommended and treated in protocols C08-002A/B and C08-003A/B were approved in 2011 for treatment of aHUS.
- The dosing regimen as per USPI and SmPC in adult and pediatric patients with aHUS resulted in a close to full inhibition of C5 by eculizumab associated with the observed efficacy.

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