THE KOREAN SOCIETY OF NEPHROLOGY
APCN & KSN 2024
June 13(Thu) - 16(Sun), 2024 Coex, Seoul, Korea
Promoting Sustainable Kidney Health: The Asia-Pacific and Beyond

Abstract Submission No.: A-0978

Rapid Complement Inhibition with the C5 Inhibitor Crovalimab: Timing Analysis Using Animal Model and Composer Trial Data

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Objectives : Atypical haemolytic uraemic syndrome (aHUS) is currently treated with the complement C5 antibodies eculizumab and ravulizumab. Although effective, regular IV infusion regimens can be burdensome. Crovalimab, a novel C5 antibody, has been engineered for small volume subcutaneous self-injection Q4W, with a weight-based dosing regimen. Crovalimab is currently being evaluated in adult and paediatric patients with aHUS in the ongoing Phase III single-arm COMMUTE-a (NCT04861259) and COMMUTE-p (NCT04958265) trials. In patients with paroxysmal nocturnal haemoglobinuria (PNH), a disease driven by uncontrolled complement activation, crovalimab maintained disease control and was well tolerated in Phase I/II and III studies. Here, in vivo models and COMPOSER data (Phase I/II [NCT03157635]; median exposure 3 years) were used to determine the time to complete complement inhibition after first crovalimab IV dose.
Methods : The pharmacokinetics/pharmacodynamics of crovalimab in cynomolgus monkeys after a single IV were assessed. Part 2 (n=10) and Part 4A (n=8) of COMPOSER enrolled patients with PNH who were complement-inhibitor naive. Free C5 and complement activity were assessed.
Results : In monkeys, a single crovalimab IV dose of 4 mg/kg reduced mean free C5 concentration by 99.6% and terminal complement activity by 81.4%, within 5 mins of administration. In treatment-naive COMPOSER patients, mean free C5 concentration dropped to <1 µg/ml, indicating a high level of target engagement within 1-6 hrs from first IV dose (Fig 1). Inhibition of terminal complement activity was reached within 1 hr, with values near or below the LLOQ (10 U/ml; Fig 2). Complete complement blockade was generally maintained long term, up to Week 20, regardless of dose.
Conclusions : Crovalimab induced a complete, rapid and sustained blockade of terminal complement activity within hours of first dose. The crovalimab regimen included an initial IV loading dose, allowing for a rapid onset of action, followed by a convenient long-term subcutaneous maintenance regimen.

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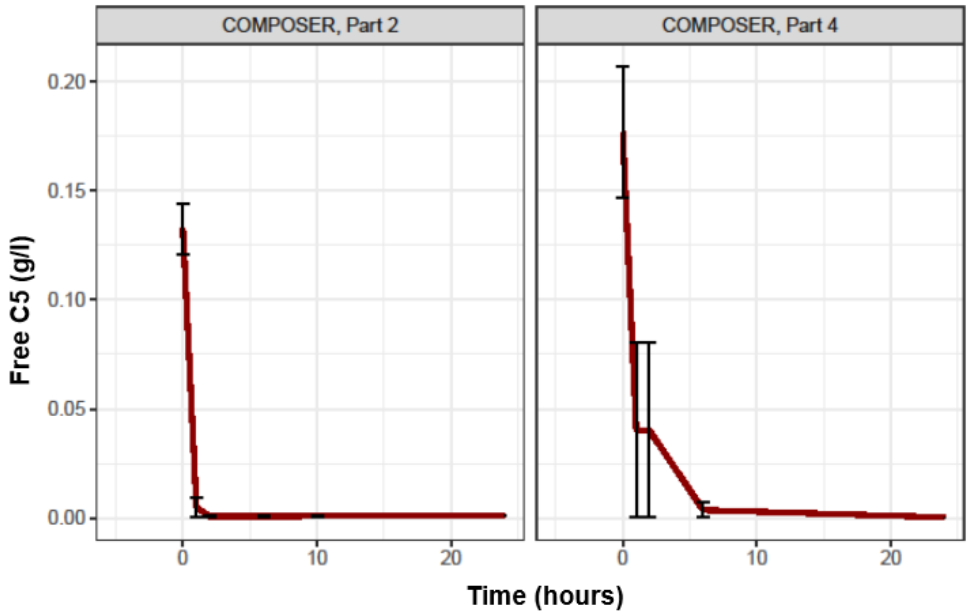
Figure 1. Mean free C5 in treatment-naive patients with PNH



The red line represents the mean and black error bars represent the standard error.

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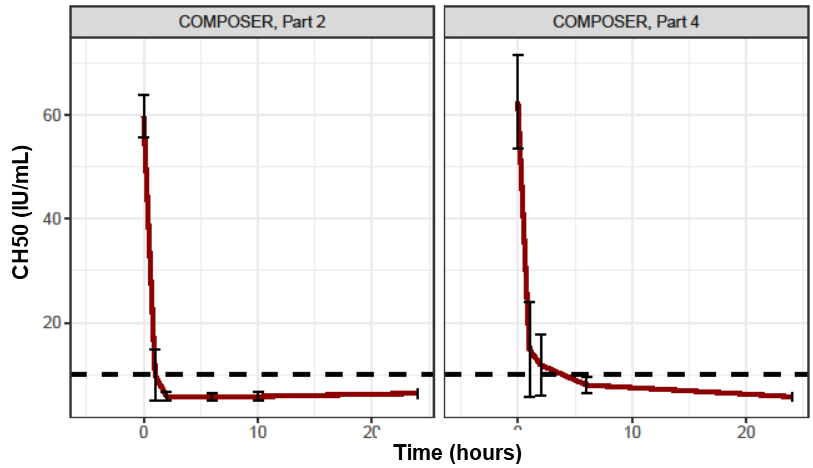
Figure 2. Mean terminal CH50 in treatment-naive patients with PNH



CH50, 50% terminal complement activity; LLOQ, lower limit of quantification.
The red line represents the mean and the black error bars represent the standard error.
The dashed black horizontal line indicates the LLOQ (10 U/mL). Values below the LLOQ were set to LLOQ/2.