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Crovalimab: patient preferences and ongoing phase III COMMUTE trials in acute haemolytic uraemic syndrome (aHUS)

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Background and Aims: aHUS is a rare, life-threatening, complement-mediated disease characterised by thrombotic microangiopathies (TMA)s. Existing C5 inhibitor (Csi) therapies, such as eculizumab (ecu) and ravulizumab (ravu), are effective for aHUS management but can be burdensome in both adults and children, typically requiring regular intravenous (IV) infusions every 2 weeks (Q2W, ecu) or every 8 weeks (ravu). Crovalimab (crova), a novel Csi with low-volume, subcutaneous (SC) administration every 4 weeks (Q4W), allows for convenient self-administration outside of a healthcare setting. Crova is currently being evaluated in two ongoing global, Phase III, single-arm trials in aHUS: COMMUTE-a (NCT04861259) and COMMUTE-p (NCT04958265). The efficacy and safety of crova have also been evaluated in patients (pts) with paroxysmal nocturnal haemoglobinuria (PNH), another complement-mediated rare blood disorder, in the global, randomised, Phase III COMMODORE 1 (NCT04432584) and COMMODORE 2 (NCT04434092) trials (Röth EHA 2023; #S181, Scheinberg EHA 2023; #S183). Here, we report pt preference data from COMMODORE 1 and 2.

Method: COMMODORE 1 and 2 enrolled Csi-experienced and Csi-naive pts with PNH, respectively. Pts were randomised 1:1 in COMMODORE 1 and 2:1 in COMMODORE 2 to receive crova (weight-based tiered dosing regimen consisting of loading doses followed by SC Q4W maintenance) or ecu (900 mg IV Q2W) over a 24-week primary treatment period. After completing 24 weeks of treatment, all pts received crova if continuing the trial. Treatment preference was assessed in adult pts using the validated Patient Preference Questionnaire (PPQ) after 17 weeks of crova treatment in Csi-experienced pts randomised to crova in COMMODORE 1 and 2. COMMUTE-a is enrolling pts with aHUS aged ≥12 years and weighing ≥40 kg (N ≥ 80), while COMMUTE-p is enrolling pts with aHUS aged ≥28 days to <18 years and weighing ≥5 kg (N ≥ 45). Both studies are enrolling 3 cohorts (Fig. 1): (1) Naive: pts not previously treated with a Csi (n ≥ 40 in COMMUTE-a; n ≥ 20 in COMMUTE-p), (2) Switch: pts switching from ecu or ravu (n ≥ 40 in COMMUTE-a; n ≥ 20 in COMMUTE-p), (3) C5 polymorphism cohort in COMMUTE-a: pts with known C5 polymorphisms (n ≤ 5); pretreated cohort in COMMUTE-p: pts previously treated with and discontinued ecu or ravu (n ≤ 10). In both COMMUTE studies, pts will receive weight-based tiered crova dosing consisting of loading doses (IV and SC) followed by SC Q4W maintenance (or Q2W if <20 kg) from Week 5 onward. The primary efficacy objective of both studies is to assess the proportion of Csi-naive pts with complete TMA response from baseline to Week 25. Secondary efficacy endpoints include change from baseline in dialysis requirement status and estimated glomerular filtration rate. Safety, pharmacokinetics, immunogenicity, biomarkers, and pt-reported fatigue will also be assessed. Treatment preference will be assessed using the PPQ in pts ≥12 years old and in caregivers of children <12 years old.

Results: 89 pts were randomised in COMMODORE 1 (crova: n = 45; ecu: n = 44) and 204 in COMMODORE 2 (crova: n = 135; ecu: n = 69). Of pts randomised to crova in COMMODORE 1, 33 (85%) of 39 pts assessed at Week 17 preferred crova over ecu. Of pts randomised to ecu who switched to crova after the primary treatment period, 27 (96%) of 28 pts who answered the questionnaire in COMMODORE 1 and 32 (84%) of 38 in COMMODORE 2 preferred crova (Fig. 2). The top reasons selected for crova preference over ecu were that the treatment required fewer hospital visits, was easier to administer, took less time to administer, and provided better quality of life (Kulasekararaj Ash 2023; #E628). COMMUTE-a and COMMUTE-p are currently open for recruitment in 17 and 14 countries, respectively.

Conclusion: Crova was preferred by ecu to by most Csi-naive and switch pts with PNH in COMMODORE 1 and 2, largely due to faster, easier administration. Crova, with SC Q4W (or Q2W in pts <20 kg with aHUS) self-administration, can potentially reduce treatment burden vs currently approved Cs is in aHUS. The COMMUTE-a and COMMUTE-p trials evaluating crova in aHUS are currently enrolling.
Figure 1: COMMUTE-a and COMMUTE-p study schema

**COMMUTE-a (NCT04861259): Adult/adolescent patients**

- Patients with aHUS aged ≥12 years and weighing ≥40 kg
  - Naive cohort (not previously treated with complement inhibitor) n=40
  - Switch cohort (switching from ecuclizumab or ravulizumab) n=40
  - CS SNP cohort (known CS polymorphism) n=5

**COMMUTE-p (NCT04958265): Paediatric patients**

- Patients with aHUS aged ≥28 days and <18 years and weighing ≥5 kg
  - Naive cohort (not previously treated with complement inhibitor) n=20
  - Switch cohort (switching from ecuclizumab or ravulizumab) n=20
  - Pre-treated cohort (previously treated with and discontinued ecuclizumab or ravulizumab) n=10

SNP, single nucleotide polymorphism. *Documented treatment for ≥60 days before Day 1 of study. # Documented treatment with ≥2 maintenance doses received prior to Day 1 of study. †Documented treatment with either ecuclizumab or ravulizumab for aHUS, with poorly controlled TMA, per investigator’s assessment. ‡Enrolment of patients weighing <40 kg will be staggered starting with patients ≥20 kg. § Received and subsequently discontinued treatment for ≥10 weeks for ecuclizumab and ≥4 weeks for ravulizumab.

Figure 2: Patient preferences in the COMMODORE 1 and COMMODORE 2 trials

**Patients randomised to crovalimab**

- Prefers ecuclizumab (3%)  - No preference (13%)
- Prefers crovalimab (85%)  - n=39#

**Patients randomised to ecuclizumab who switched to crovalimab in the extension period**

- Prefers crovalimab (96%)  - n=28#
- Prefers ecuclizumab (84%)  - n=38#

Patients were assessed after 17 weeks of crovalimab. *Only patients with available data (having completed the questionnaire) were included in the calculations of percentages. Kulasekaranaj ASH 2023; #5628.