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ORAL ABSTRACTS

508.BONE MARROW FAILURE: ACQUIRED

Safety of Crovalimab Versus Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH): Pooled Results from the Phase III COMMODORE 1, COMMODORE 2, and COMMODORE 3 Studies

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Introduction

Crovalimab (crova) is a novel anti-C5 recycling antibody that allows for low-volume, subcutaneous (SC) self-administration every 4 weeks (q4w). The single arm COMMODORE 3 study (NCT04654468) in C5 inhibitor (C5i)-naive patients (pts) with PNH in China was the first Phase III study to show that crova is efficacious and well tolerated (primary analysis; Liu Am J Hematol 2023), and confirmed these findings after 6 additional months of crova exposure (Liu EHA 2023; #P785). COMMODORE 1 (NCT04432584) and COMMODORE 2 (NCT04434092) are global, randomized, open-label, multicenter, Phase III trials that evaluated crova versus eculizumab (ecu) in C5i-experienced and -naive pts with PNH, respectively. COMMODORE 2 demonstrated non-inferior efficacy for crova versus ecu, with a safety profile consistent between crova and ecu (Röth EHA 2023; #S181). COMMODORE 1 supported the favorable benefit-risk profile of crova (Scheinberg EHA 2023; #S183). Here, we report pooled safety data for crova and ecu from COMMODORE 1, 2, and 3.

Methods

In COMMODORE 1, C5i-experienced pts who were receiving ecu were randomized 1:1 to receive crova or ecu. Pts with the C5 polymorphism or receiving ravulizumab or high-dose ecu, and pediatric pts receiving ecu were enrolled in a descriptive arm to receive crova. In COMMODORE 2, C5i-naive pts were randomized 2:1 to receive crova or ecu. Pediatric pts were enrolled in a descriptive arm to receive crova. In COMMODORE 3, C5i-naive pts received crova. In all 3 studies, crova was administered per a weight-based tiered dosing approach that included loading doses followed by SC q4w maintenance. Ecu was given intravenously every 2 weeks. The primary treatment period was 24 weeks for all 3 studies; all pts continuing after Week 25 received crova.

Safety data from the 3 studies were pooled and assessed by C5i-naive versus -switched status and in total.

Results

Safety data from 488 pts (crova, n=377 [naive, n=192; switched, n=185]; ecu, n=111) were analyzed. Baseline characteristics for the pooled population were generally balanced between the crova and ecu arms, and between the C5i-naive and

-switched groups for crova. Median age at baseline was 38 y (range, 13–85) in the crova population and 44 y (17–85) in the ecu population, with 11 (3%) pts and 2 (2%) pts aged <18 y at enrollment, respectively. The median time from PNH diagnosis to enrollment was 4.8 y (range, 0.0-50.3) in crova pts and 5.7 y (range, 0.0-31.0) in ecu pts. At baseline, 38% of crova pts and 37% of ecu pts had a history of aplastic anemia; 3% and 5% of pts had myelodysplastic syndrome, respectively.

At the respective clinical cutoff dates, the median treatment duration was 44.4 weeks for crova pts and 22.1 weeks for ecu pts (Table 1). There were 522 adverse events (AEs) per 100 pt years (PY) in crova pts and 583 in ecu pts. There were 7.4 serious infections per 100 PY in crova pts (6.1 naive; 9.3 switched) and 14.1 in ecu pts, with no meningococcal infections. The proportion of pts with common AEs and serious AEs is shown in Table 2. A higher percentage of C5i-naive pts appeared to experience AEs than C5i-switched pts or ecu pts, due to the inclusion of pts with a longer treatment duration from the single-arm COMMODORE 3 study in the C5i-naive group. Fatal AEs occurred in 4 (1%) crova pts (3 naive; 1 switched) and 1 (1%) ecu pt, all unrelated to treatment (Table 1). AEs leading to treatment discontinuation occurred in 1% of crova pts (1% naive; 2% switched) and 1% of ecu pts. 4% of crova pts (4% naive; 4% switched) and 3% of ecu pts had ≥1 AE leading to dose modification or interruption.

In crova switched pts only, complexes formed with other C5i could lead to one-time Type III hypersensitivity (T3H) reactions, which occurred in 18% of switched pts. The median time to onset of the T3H reaction was 1.6 weeks (range, 0.7-4.4) and the median duration of T3H reactions was 1.9 weeks (0.4-34.1). The most frequently reported (≥5%) manifestations of T3H reactions were arthralgia (9%) and rash (6%); no pt had renal manifestations. Most T3H reactions were Grade 1-2; Grade 3 events occurred in 7% of switched pts. One pt discontinued crova due to a Grade 3 T3H.

The safety profile was consistent between pediatric and adult pts.

Conclusions

Overall, pooled safety data from COMMODORE 1, 2, and 3 showed that the safety profile of crova was consistent with that of ecu in pts with PNH, and comparable between pts who were C5i-naive and switched from C5i to crova.

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Table 1. Overview of adverse events

	Crova			Ecu
	C5i naive (n=192; 196.1 PY)	Switched from C5i to crova (n=185; 139.9 PY)	Total (n=377; 336.0 PY)	(n=111; 49.8 PY)
Treatment duration, median (range), weeks	52.1 (0.1–107.9)	32.3 (0.3–108.4)	44.4 (0.1–108.4)	22.1 (0.1–26.1)
AEs per 100 PY (95% CI)	542 (510, 576)	495 (459, 533)	522 (498, 547)	583 (518, 654)
Treatment-related AE	216 (196, 237)	111 (94, 130)	172 (158, 187)	141 (110, 178)
Grade 3–5 AE	61 (51, 73)	54 (43, 68)	58 (50, 67)	50 (33, 74)
Fatal AE	1.5 (0.3, 4.5)[a]	0.7 (<0.1, 4.0)[b]	1.2 (0.3, 3.0)	2.0 (<0.1, 11.2)[c]
Serious AE	21 (15, 28)	31 (22, 41)	25 (20, 31)	32 (18, 52)
Treatment-related serious AE	3.6 (1.4, 7.4)	5.0 (2.0, 10.3)	4.2 (2.3, 7.0)	2.0 (0.1, 11.2)
AE leading to withdrawal from treatment	0.5 (<0.1, 2.8)[d]	2.2 (0.4, 6.3)[e]	1.2 (0.3, 3.0)	2.0 (0.1, 11.2)[c]
Treatment-related AE leading to withdrawal from treatment	0.5 (<0.1, 2.8)	1.4 (0.2, 5.2)	0.9 (0.2, 2.6)	0 (NE, 7.4)
AE leading to dose modification or interruption	5.1 (2.5, 9.4)	5.7 (2.5, 11.3)	5.4 (3.2, 8.5)[f]	6.0 (1.2, 17.6)[g]
Treatment-related AE leading to dose modification or interruption	1.0 (0.1, 3.7)	2.9 (0.8, 7.3)	1.8 (0.7, 3.9)	0 (NE, 7.4)

AE, adverse event; C5i, C5 inhibitor; crova, crovalimab; ecu, eculizumab; NE, not estimable; PY, patient years. Clinical cutoff: Nov 16, 2022 (COMMODORE 1 and COMMODORE 2); August 10, 2022 (COMMODORE 3).
[a] n=3; myocardial infarction before the start of treatment, respiratory hemorrhage after treatment discontinuation, and subdural hematoma. [b] n=1; colorectal cancer. [c] n=1; ischemic stroke, not related to ecu. [d] n=1; Grade 4 serious AE of thrombocytopenia, related to crova. [e] n=3; Grade 3 serious AE of demyelinating polyneuropathy (not related to crova), Grade 3 serious AE of T3H reaction (related to crova), Grade 3 serious AE of sepsis (related to crova). [f] Most common AEs leading to dose modification were COVID-19 (n=5), T3H reaction (n=2), and infusion-related reaction (n=2). [g] Sepsis, cholecystitis chronic, and COVID-19, n=1 each.

Table 2. AEs and serious AEs in ≥10% and ≥1% of patients, respectively, in any group

	Crova			Ecu
	C5i naive (n=192)	Switched from C5i to crova (n=185)	Total (n=377)	(n=111)
AEs in ≥10% of patients in any group, n (%)				
Upper respiratory tract infection	45 (23)	10 (5)	55 (15)	10 (9)
Neutrophil count decreased	36 (19)	5 (3)	41 (11)	7 (6)
White blood cell count decreased	31 (16)	8 (4)	39 (10)	7 (6)
COVID-19	29 (15)	32 (17)	61 (16)	11 (10)
Infusion-related reaction[a]	23 (12)	17 (9)	40 (11)	9 (8)
Pyrexia	22 (11)	21 (11)	43 (11)	8 (7)
Headache	16 (8)	21 (11)	37 (10)	4 (4)
T3H reaction	NA[b]	33 (18)[c]	NA[b]	NA[b]
Serious AEs in ≥1% of patients in any group, n (%)				
Pneumonia	4 (2)	1 (1)	5 (1)	1 (1)
Aplastic anemia	2 (1)	0	2 (1)	1 (1)
Epistaxis	2 (1)	0	2 (1)	0
Thrombocytopenia	2 (1)	0	2 (1)	1 (1)
Upper respiratory tract infection	2 (1)	0	2 (1)	0
COVID-19	1 (1)	2 (1)	3 (1)	1 (1)
Breakthrough hemolysis	1 (1)	2 (1)	3 (1)	0
T3H reaction	NA[b]	5 (3)[c]	NA[b]	NA[b]
Urinary tract infection	0	2 (1)	2 (1)	1 (1)

AE, adverse event; C5i, C5 inhibitor; crova, crovalimab; ecu, eculizumab; NA, not applicable.
Clinical cutoff: Nov 16, 2022 (COMMODORE 1 and COMMODORE 2); August 10, 2022 (COMMODORE 3).
[a] All events were Grade 1–2. The most frequently reported symptoms of infusion-related reactions were headache (7%; 9% naive, 6% switched) and rash (1%; 1% naive, 1% switched) in the crova population, and headache (5%) in the ecu population. [b] Only manifests due to drug–target–drug complex formation in patients who switched between crova and other C5i. [c] All patients who switched from another C5 inhibitor at baseline or after the primary treatment period were clinically evaluated for the manifestations of T3H reactions.

Figure 1

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