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POSTER ABSTRACTS

508.BONE MARROW FAILURE: ACQUIRED

Biomarker Analyses in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Treated with Crovalimab and Eculizumab: Results from the Phase III Randomized COMMODORE 2 Trial

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Introduction

PNH is a hematopoietic stem cell disorder characterized by hemolytic anemia, hemoglobinuria, and increased risk of thromboembolic events, and is associated with bone marrow failure. Crovalimab (crova) is a novel complement C5 inhibitor engineered with recycling technology, with a long half-life and high solubility that enables low-volume subcutaneous (SC) administration every 4 weeks (q4w). The global Phase III COMMODORE 2 study (NCT04434092) in C5 inhibitor-naive patients (pts) with PNH demonstrated non-inferiority of crova vs eculizumab (ecu) for hemolysis control, transfusion avoidance, breakthrough hemolysis, and hemoglobin stabilization, and a safety profile that was consistent between crova and ecu (Röth EHA 2023; #S181). Here we report results of the exploratory biomarker analyses in COMMODORE 2.

Study Design and Methods

In COMMODORE 2, C5 inhibitor-naive pts were randomized 2:1 to receive a weight-based tiered crova regimen or ecu. Regimens included loading doses, followed by maintenance dosing (crova: SC injection q4w; ecu: intravenous infusion every 2 weeks). Co-primary efficacy endpoints were proportion of pts with hemolysis control (central lactate dehydrogenase [LDH] ≤1.5×upper limit of normal [ULN]) from Week (W)5 through W25 and proportion of pts with transfusion avoidance from baseline through W25. Exploratory biomarker analyses included terminal complement activity per 50% hemolytic complement (CH50) liposome immunoassay, free hemoglobin, additional exploration of LDH levels, and flow cytometry of the PNH clone size/C3d levels. Additional descriptive analyses of hemoglobin data compared pts with and without transfusions. All biomarker data were assessed from baseline to W25.

Results

Data forCH50 and LDH were available for all 204 randomized pts (crova: 135; ecu: 69) and data for free hemoglobin, PNH clone size and C3d were available for 126 pts (crova: 85; ecu: 41). At baseline, mean (standard deviation [SD]) LDH levels were 7.6×ULN (3.4) in crova pts and 7.8×ULN (3.5) in ecu pts. 77% of crova pts and 74% of ecu pts had ≥1 packed red blood cell transfusion ≤12 months before screening. 39% of crova pts and 38% of ecu pts had a history of aplastic anemia; 4% and 9% had myelodysplastic syndrome, respectively.

Inhibition of complement activity (per CH50) to below the lower limit of quantification was reached at W2 (first post-dose pharmacodynamic sample) in 93% and 46% of pts in the crova and ecu arms, respectively, and in 90% and 73% at W25 (post-dose) (Figure). With regards to intravascular hemolysis markers, the proportion of pts with LDH ≤1.5×ULN was 81% at W5 and 78% at W25 in crova pts, and 84% at W5 and 77% at W25 in ecu pts. Free hemoglobin, another intravascular hemolysis marker,

showed a similar initial decrease from baseline in both arms; however, crova pts consistently showed numerically lower levels than ecu pts from W13 to W25.

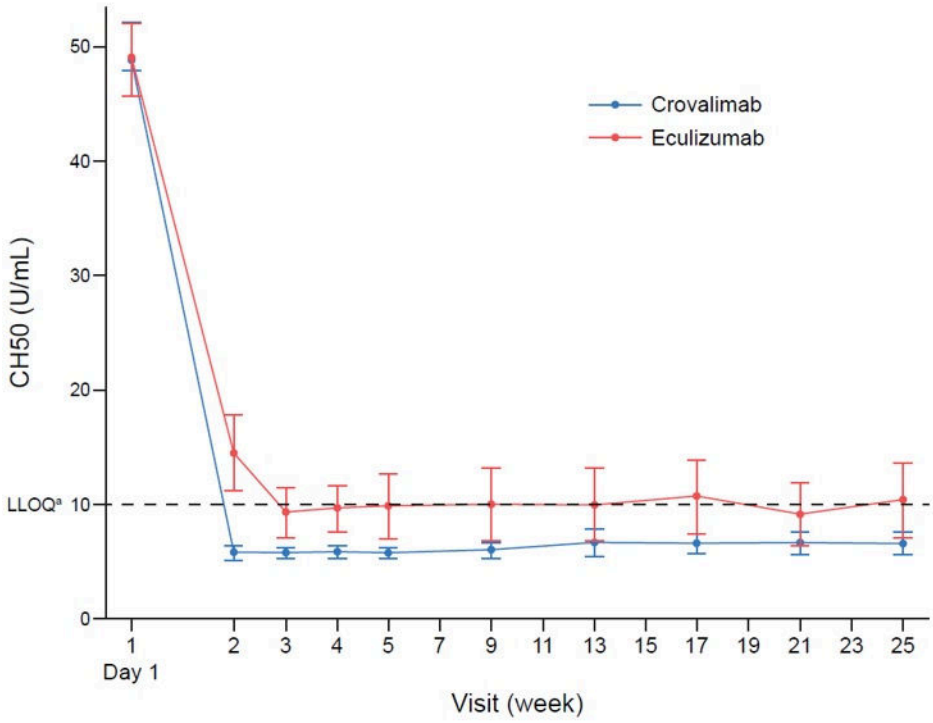
Mean (SD) increase in hemoglobin level from baseline to W25 was 1.2 g/dL (2.0) in the crova arm (baseline: 8.7 g/dL [1.4]) and 0.8 g/dL (1.9) in the ecu arm (baseline: 8.9 g/dL [1.4]). In both arms, a greater increase in mean hemoglobin level from baseline was observed in pts who achieved transfusion avoidance vs those requiring ≥1 transfusion up to W25 (crova: 1.7 g/dL [SD, 1.8; n=88] vs 0.2 g/dL [SD, 1.9; n=40]; ecu: 1.3 g/dL [SD, 1.6; n=47] vs −0.4 g/dL [SD, 2.1; n=20]). Both arms showed a similar increase from baseline to W25 in the mean (SD) percentage of C3d-positive PNH erythrocytes (crova: 0.7 [1.5] at baseline to 20.8 [19.1] at W25; ecu: 0.6 [0.9] to 22.3 [15.0]).

Conclusions

Treatment with crova or ecu reduced terminal complement activity effectively, with a higher proportion of crova than ecu pts having undetectable terminal complement activity. However, this did not translate into significant differences in other biomarkers (LDH and free hemoglobin) or in the clinical efficacy between crova and ecu arms. Hemoglobin levels increased in both crova and ecu arms. This improvement was more pronounced in pts not receiving a transfusion from baseline to W25; additional analysis is needed to elucidate the impact of bone marrow failure status. Similar increases in C3d level in each arm were expected, as this is a C5 inhibitor class phenomenon. Overall, biomarker data from COMMODORE 2 support the non-inferior efficacy of crova vs ecu in patients with PNH. Further analyses correlating additional biomarkers with clinical outcomes is warranted.

Disclosures Lundberg: *F. Hoffmann-La Roche Ltd, Basel:* Current Employment, Current equity holder in publicly-traded company. **de la Iglesia:** *Hospital Universitario de Gran Canaria Doctor Negrín:* Current Employment, Ended employment in the past 24 months; *Novartis:* Consultancy; *BMS:* Consultancy. **Kelly:** *Novartis:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Abbvie:* Membership on an entity's Board of Directors or advisory committees; *Alexion:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Astellas:* Honoraria, Speakers Bureau; *Amgen:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Biologix:* Honoraria, Speakers Bureau; *Jazz:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Pfizer:* Honoraria, Speakers Bureau; *Sobi:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Kulasekararaj:** *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Celgene/BMS:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *BioCryst:* Consultancy; *Achillion:* Consultancy; *Amgen:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Akari Therapeutics:* Consultancy; *Samsung:* Consultancy; *Alexion, AstraZeneca Rare Disease:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *F. Hoffmann-La Roche Ltd:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Nishimura:** *Chugai Pharmaceutical Co., Ltd:* Membership on an entity's Board of Directors or advisory committees; *Alexion, AstraZeneca Rare Disease:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Roche:* Membership on an entity's Board of Directors or advisory committees. **Risitano:** *Novartis:* Consultancy, Honoraria; *F. Hoffmann-La Roche Ltd:* Consultancy, Honoraria, Research Funding; *Alexion, AstraZeneca Rare Disease:* Consultancy, Honoraria, Research Funding. **Roeth:** *Apellis Apellis Pharmaceuticals:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria; *Bioverativ:* Consultancy, Honoraria; *Sanofi:* Consultancy, Honoraria; *Roche:* Consultancy, Honoraria, Research Funding; *Biocryst:* Consultancy, Honoraria; *Alexion, AstraZeneca Rare Disease:* Consultancy, Honoraria. **Buatois:** *F. Hoffmann-La Roche Ltd:* Current Employment, Current equity holder in publicly-traded company. **Chebon:** *F. Hoffmann-La Roche Ltd:* Current Employment. **Patel:** *Genentech, Inc.:* Current Employment. **Kiialainen:** *F. Hoffmann-La Roche Ltd:* Current Employment, Current equity holder in publicly-traded company.

Figure. Inhibition of complement activity per CH50.



CH50, 50% hemolytic complement activity measured by liposome immunoassay; LLOQ, lower limit of quantification. Clinical cutoff: November 16, 2022.
Data plotted are mean (standard error).[a] Per liposome immunoassay.

Figure 1

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