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RESEARCH ARTICLE

Phase 3 randomized COMMODORE 1 trial: Crovalimab versus eculizumab in complement inhibitor-experienced patients with paroxysmal nocturnal hemoglobinuria

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Abstract

Crovalimab, a novel C5 inhibitor, allows for low-volume, every-4- week, subcutaneous self-administration. COMMODORE 1 (NCT04432584) is a phase 3, global, randomized trial evaluating crovalimab versus eculizumab in C5 inhibitor-experienced

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patients with paroxysmal nocturnal hemoglobinuria (PNH). Adults with lactate dehydrogenase ≤1.5 × upper limit of normal and receiving approved eculizumab doses for ≥24 weeks were randomized 1:1 to receive crovalimab (weight-based tiered dosing) or continue eculizumab. The original primary study objective was efficacy; however, given the evolving treatment landscape, target recruitment was not met, and all efficacy endpoints became exploratory, with safety as the new primary objective. Exploratory efficacy endpoints included transfusion avoidance, hemolysis control, breakthrough hemolysis, hemoglobin stabilization, FACIT-Fatigue score, and patient preference (crovalimab vs. eculizumab). Eighty-nine patients were randomized (45 to crovalimab; 44 to eculizumab). During the 24-week primary treatment period, adverse events (AEs) occurred in 77% of patients receiving crovalimab and 67% receiving eculizumab. No AEs led to treatment withdrawal or death, and no meningococcal infections occurred. 16% of crovalimab-treated patients had transient immune complex reactions (also known as Type III hypersensitivity events), an expected risk when switching between C5 inhibitors that bind to different C5 epitopes; most were mild/moderate and all resolved without treatment modification. Crovalimab-treated patients had sustained terminal complement activity inhibition, maintained disease control, and 85% preferred crovalimab over eculizumab. Together with phase 3 COMMODORE 2 results in complement inhibitor-naive patients, these data support crovalimab's favorable benefit–risk profile. Crovalimab is a new C5 inhibitor for PNH that is potentially less burdensome than existing therapies for this lifelong disease.

1 | INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, clonal hematologic disorder[1–3] caused by a somatic mutation in hematopoietic stem cells' phosphatidylinositol glycan class A (PIGA) gene.[4,5] This increases the susceptibility of affected PNH cells to complement-mediated lysis, resulting in chronic intravascular hemolysis and anemia.[3,6] Disease complications include thromboembolic events, impairment of renal function, abdominal pain, and pulmonary arterial hypertension.[1] Thromboembolic events are the primary cause of death in people with PNH who do not receive adequate treatment.[3,7,8] PNH is life-threatening in patients who are not adequately treated, with a 20-year survival rate of 69% in patients never treated with a C5 inhibitor.[9] Additionally, these patients can have a poor quality of life.[10]

Eculizumab and ravulizumab, terminal complement inhibitors that target C5, are effective and well-tolerated PNH treatments, reducing intravascular hemolysis, reducing thrombosis risk, and increasing survival outcomes.[11–15] In the 301 and 302 studies, ravulizumab achieved non-inferiority to eculizumab for all efficacy endpoints, with a numerically lower number of breakthrough hemolysis events.[12,13] These terminal complement inhibitors have become the standard of care for PNH in countries where they are available, supported by long-term data from randomized trials and over 15 years of real-world evidence.[16] However, the need for frequent IV infusions with eculizumab (every 2 weeks) can interfere with work, education, travels, daily schedules and impact patients' quality of life.[17–19] Although the introduction of ravulizumab, a C5 inhibitor with an extended half-life versus eculizumab, addressed some of these gaps, there remains a need for additional therapeutic options to reduce treatment burden and increase patient convenience in the context of this lifelong disease.

Crovalimab is a novel humanized anti-C5 recycling monoclonal antibody that was engineered with Sequential Monoclonal Antibody Recycling Technology (SMART-Ig) and designed with a long half-life, high bioavailability, and high solubility. This supports low-volume, every-4-weeks, subcutaneous administration, resulting in rapid, complete, and sustained C5 inhibition.[20,21] Crovalimab binds to an epitope on the C5 β chain, unlike eculizumab and ravulizumab that bind to the C5 α chain,[20] which allows crovalimab to be additionally effective in patients with a C5 R885H polymorphism, who respond poorly to eculizumab and ravulizumab.[12,22]

Results of the phase 1/2 COMPOSER study showed that crovalimab was well tolerated and efficacious over a 3-year median treatment duration in patients with PNH; it achieved rapid and sustained C5 inhibition and disease control in C5 inhibitor-naive patients, while maintaining disease control in patients switching from eculizumab.[23] Additionally, the global, randomized, multicenter, phase 3 COMMODORE 2 trial in C5 inhibitor-naive patients with PNH demonstrated the non-inferiority of crovalimab versus eculizumab for the co-primary endpoints of hemolysis control and transfusion avoidance; the trial showed similar, well-tolerated safety profiles for crovalimab and eculizumab.[24] These results are supported by data from the single-arm phase 3 COMMODORE 3 trial evaluating the efficacy and safety of crovalimab in Chinese patients who were C5 inhibitor naive.[25]

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Here, we present the results of the randomized, phase 3 COMMODORE 1 study that evaluated the safety, pharmacodynamics, pharmacokinetics, and exploratory efficacy of crovalimab versus eculizumab in C5 inhibitor-experienced patients with PNH.

2 | METHODS

2.1 | Study design

COMMODORE 1 (NCT04432584) is a global, randomized, open-label, multicenter, phase 3 trial evaluating crovalimab versus eculizumab in patients with PNH who had adequately controlled intravascular hemolysis on approved eculizumab dosing. Patients were enrolled from 70 sites in 25 countries (Supplemental Table 1). Protocol approval was obtained from each site's institutional review board or ethics committee. COMMODORE 1 was conducted according to the International Council on Harmonization Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. All patients provided written informed consent. All authors had access to primary clinical trial data. The study sponsor supplied the study drugs and collaborated with academic authors on the study design, data collection, data analysis, and data interpretation.

The study consisted of a 4-week screening period and a 24-week primary treatment period, where patients were randomized 1:1 to receive crovalimab or eculizumab, with randomization stratified by history of packed red blood cell (pRBC) transfusion in the previous 12 months (yes vs. no) (Supplemental Figure 1). This was followed by an extension period, during which patients randomized to crovalimab could continue crovalimab treatment, and patients randomized to eculizumab could switch to crovalimab. If a patient discontinued study treatment at any time, they entered a safety follow-up period.

COMMODORE 1 was initially designed to enroll ≈200 patients with PNH into the randomized arms to evaluate the efficacy of crovalimab versus eculizumab and ≈50 patients with PNH in the non-randomized arm. However, given the evolving treatment landscape, with a reduced pool of patients treated with eculizumab over time, randomization was terminated in November 2022. With this change, the initially targeted sample size for the randomized arms could not be reached, providing insufficient statistical power for efficacy analyses. Therefore, all efficacy endpoints became exploratory, and safety became the new primary objective. Following the termination of the randomized arms, the non-randomized arm (see Supplemental Material for further details) was additionally opened to patients who had been receiving eculizumab at the approved dose, to allow continued access to crovalimab for this population in a non-randomized setting. The sample size for this non-randomized arm was increased, and enrollment is ongoing.

2.2 | Patient population

In this study, adult patients (≥18 years old, weighing ≥40 kg) were eligible for inclusion into the randomized arms if they had a documented diagnosis of PNH, confirmed by high-sensitivity flow cytometry, with granulocyte or monocyte GPI-deficient clone size ≥10%. Patients enrolled were receiving approved dosing of eculizumab (900 mg every 2 weeks) for ≥24 weeks prior to the first study drug administration and had lactate dehydrogenase (LDH) levels of ≤1.5 × the upper limit of normal (ULN) at screening. All patients must have had a platelet count of >30 000/mm^3 and an absolute neutrophil count of >500/mm^3. Patients were excluded if they had major adverse vascular events in the 6 months prior to first study of drug administration or history of *Neisseria meningitidis* infection within 6 months prior to screening and up to the first study drug administration. Vaccination against *Neisseria meningitidis* serotypes A, C, W, and Y within 3 years before study treatment initiation was required. Detailed eligibility criteria are presented in the Supplemental Appendix.

2.3 | Interventions

Patients randomized to crovalimab received a weight-based tiered dosing regimen of crovalimab, including a loading series (IV dose on Day 1 followed by weekly subcutaneous doses on Days 2, 8, 15, and 22) and maintenance dosing (subcutaneous doses every 4 weeks starting Day 29; Supplemental Figure 1). Patients randomized to eculizumab continued on the approved maintenance dose of eculizumab (900 mg IV every 2 weeks).

Crovalimab self-administration or administration by a caregiver was permitted starting at Week 9 after they were trained and had their proficiency confirmed by a healthcare professional. Patients who did not wish to self-inject or have a caregiver administer crovalimab could continue to have crovalimab administered by the investigator or other study site staff.

2.4 | Study endpoints and assessments

The primary objective of this study was to evaluate the safety and tolerability of crovalimab versus eculizumab. Safety endpoints included incidence and severity of adverse events (AEs), with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5 (CTCAE v5); incidence and severity of injection site reactions, infusion-related reactions, hypersensitivity, and infections (including meningococcal meningitis); and incidence and severity of clinical manifestations of transient immune complex reactions (also known as Type III hypersensitivity reactions) in patients who switched from eculizumab to crovalimab. During the 24-week primary treatment period, all patients (in both the crovalimab and eculizumab arms) had scheduled clinic visits weekly during the loading phase and then every 2 weeks starting at Week 5, at which patients were examined for AEs. All AEs and serious AEs were recorded during the study and for 46 weeks (approximately 10.5 months) after the last dose of crovalimab and 10 weeks after the last dose of eculizumab.

Pharmacokinetic endpoints included serum concentrations of crovalimab over time. Pharmacodynamic endpoints included change over

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time in complement activity (CH50, 50% hemolytic complement) measured by liposome immunoassay (LIA), total C5 concentration, and free C5 concentration. Free C5 levels were only assessed in the crovalimab arm as the bioanalytical assay used to quantify free C5 is specific to crovalimab-free C5 (Supplemental Methods).

Exploratory efficacy endpoints included the proportion of patients maintaining hemolysis control (centrally assessed LDH ≤1.5 × ULN), achieving transfusion avoidance (pRBC transfusion-free), having a breakthrough hemolysis event (≥1 new or worsening symptom or sign of intravascular hemolysis [fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia [hemoglobin <10 g/dL], a major adverse vascular event including thrombosis, dysphagia, or erectile dysfunction] in the presence of elevated LDH >2 × ULN after prior reduction of LDH to ≤1.5 × ULN on treatment), with hemoglobin stabilization (avoidance of a ≥2 g/dL decrease in hemoglobin level from baseline, in the absence of transfusion), and experiencing a major adverse vascular event.

Additional exploratory endpoints included mean change in fatigue from baseline to Week 25, assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) score[26] and patient preference for crovalimab versus eculizumab treatment after 17 weeks of crovalimab treatment.

The proportion of subcutaneous administrations by patient or caregiver (at home or in the clinic) after Week 9 was also assessed.

2.5 | Statistical analyses

Safety was assessed in the safety-evaluable population, which included all enrolled patients who received ≥1 dose of study drug. Safety results are reported for the primary safety period, which was from baseline to Week 25 for crovalimab and from baseline to Week 25 (or at the time of switch to crovalimab in the extension) for eculizumab. All safety endpoints were analyzed descriptively and grouped by treatment received.

Pharmacokinetics and pharmacodynamics were assessed in all patients who received ≥1 dose of study treatment and had ≥1 post-dose concentration result for crovalimab/eculizumab (pharmacokinetics) or ≥1 biomarker sample (pharmacodynamics). Results are reported from baseline to Week 25.

Exploratory efficacy was assessed in the efficacy-evaluable population, which included patients who were randomized ≥24 weeks before the clinical cutoff date, received ≥1 dose of crovalimab or eculizumab, and had ≥1 central LDH level assessment after the first IV infusion. Efficacy data are reported from baseline through Week 25. Weighted differences in proportions of patients with transfusion avoidance, breakthrough hemolysis, and hemoglobin stabilization were computed using Mantel–Haenszel weights, and 95% CIs were estimated using the stratified Newcombe method.[27] For these three binary endpoints, patients who discontinued treatment before completing the primary treatment period were conservatively assumed to have experienced the unfavorable outcome. For hemolysis control, a generalized estimating equation model was used to estimate the adjusted log-odds ratio of central LDH ≤1.5 × ULN between the crovalimab and eculizumab arms, taking into account the intra-individual correlation between central LDH values across visits and adjusting for baseline covariates. The 95% CIs for the proportions of patients with transfusion avoidance, breakthrough hemolysis, and hemoglobin stabilization were calculated using Wilson's method with continuity correction.

Fatigue was assessed by changes in the FACIT-Fatigue, a 13-item measure that evaluates self-reported fatigue and its impact on daily activities and function, in patients aged ≥18 years old.[26] Total FACIT-Fatigue scores can range from 0 to 52, with higher scores indicating lower fatigue severity and a positive change from baseline indicating an improvement.[26] Mean adjusted change in FACIT-Fatigue score from baseline to Week 25 was estimated using a mixed-effect model for repeated measures.

Patient preference for crovalimab versus eculizumab was assessed using a two-item questionnaire developed by the sponsor (Supplemental Methods). Patients randomized to the crovalimab arm who received 17 weeks of treatment were asked to indicate their preference for IV eculizumab or subcutaneous crovalimab and the top three reasons for their preference.

The proportion of administrations by patients and caregivers was summarized from Week 9 to Week 25 in those trained and confirmed by the healthcare professional to be proficient in administering crovalimab subcutaneously.

All statistical analyses are descriptive. Further details are provided in Supplemental Methods.

3 | RESULTS

This primary analysis of data from the COMMODORE 1 randomized arms has a clinical cutoff date of November 16, 2022, for the 24-week primary treatment period. The first patient was enrolled on June 16, 2020.

3.1 | Patient disposition and baseline characteristics

Of 146 patients screened for eligibility across all arms, 89 were randomized (crovalimab arm, $n = 45$; eculizumab arm, $n = 44$) (Supplemental Figure 2). Three randomized patients did not receive study treatment, including one patient randomized to crovalimab (withdrawal by patient) and two patients to eculizumab (withdrawal by patient [$n = 1$] and physician decision [$n = 1$]). Five patients in each arm had been randomized <24 weeks before the clinical cutoff date and were therefore still ongoing in the primary treatment period. Details on study disposition are available in Supplemental Figure 2. Baseline characteristics were generally well balanced between arms (Supplemental Table 2). Thirty-three percent of patients in the crovalimab arm and 36% in the eculizumab arm had a history of aplastic anemia; no patients in either arm had a history of myelodysplastic syndrome.

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3.2 | Safety

The safety-evaluable population included 44 patients receiving crovalimab and 42 receiving eculizumab. Seventy-seven percent of patients (34 of 44) treated with crovalimab, and 67% (28 of 42) treated with eculizumab had ≥1 AE in the primary safety period (Table 1). The most common AEs reported in ≥5% of patients of either arm were pyrexia (16% with crovalimab vs. 2% with eculizumab), COVID-19 (14% vs. 17%), and infusion-related reactions (14% vs. 0%; infusion-related reactions are less likely to occur in patients already stabilized on eculizumab), respectively (Supplemental Table 3). The most common symptom of infusion-related reactions was headache (5%). AEs that occurred exclusively in the crovalimab arm due to switch from eculizumab or subcutaneous administration were transient immune complex reactions (16%) and injection site reactions (9%; Supplemental Table 4), respectively. All injection site reactions and infusion-related reactions were mild or moderate, nonserious, and resolved without dose modification or interruption of crovalimab.

Transient immune complex (also known as drug-target-drug-complexes) reactions occurred in seven participants in the crovalimab arm at the time of switching from eculizumab to crovalimab, due to each C5 inhibitor binding to a different C5 epitope.[28] All transient immune complex reactions were treatment-related and all were mild or moderate except for one patient who experienced a severe event; no life-threatening or fatal events were reported. Time to onset of transient immune complex reactions ranged from 9 to 15 days.

The most common manifestations of transient immune complex reactions were rash ($n = 5$; 11%), and arthralgia and/or myalgia ($n = 5$; 11%; Table 2), with no evidence of renal involvement. The one patient with a severe transient immune complex reaction had symptoms of arthralgia, dizziness, abdominal pain, and nausea. All transient immune complex reactions resolved with no change in crovalimab treatment. Treatments used for mild/moderate reactions were mainly analgesics or nonsteroidal anti-inflammatories for arthralgia, and antihistamines and topical steroids for rash; systemic steroids were also used for the severe reaction.

Serious AEs occurred in 14% ($n = 6$) and 2% ($n = 1$) of patients treated with crovalimab and eculizumab, respectively; none were treatment-related (Table 1). No AEs led to withdrawal from the study, and no fatal AEs occurred during the primary treatment period. One

TABLE 1 Safety summary.

	Crovalimab ($n = 44$)	Eculizumab ($n = 42$)
Median treatment duration (range), weeks[a]	20.1 (2.1–22.3)	22.1 (0.1–26.1)
Median number of doses received (range)	10.0 (4.0–11.0)	12.0 (1.0–14.0)
Patients with ≥1 AE, *n* (%)		
Any-grade AE	34 (77)	28 (67)
Grade 3/4 AE	8 (18)	1 (2)
AE leading to death	0	0
AE leading to treatment withdrawal	0	0
Serious AE	6 (14)[b]	1 (2)[c]
AE leading to treatment modification/interruption	1 (2)[d]	0
Patients with ≥1 AE related to treatment, *n* (%)		
Any-grade AE	14 (32)	0
AE leading to treatment withdrawal	0	0
Serious AE	0	0

[a]The treatment duration is calculated as the date of the last study-drug administration (Week 21 in the crovalimab arm, and Week 23 in the eculizumab arm) minus the date of the first study drug administration (Week 1) plus 1 day.
[b]Six patients reported eight events (infections [$n = 3$], neutropenia [$n = 1$], pyrexia [$n = 1$], hyperbilirubinemia [$n = 1$], skin laceration [$n = 1$], and cervical dysplasia [$n = 1$]).
[c]One patient reported three events (infections [$n = 2$] and transient ischemic attack [$n = 1$]).
[d]Pneumonia; not related to treatment.

TABLE 2 Manifestations of transient immune complex reactions.

	Crovalimab ($n = 44$)	
	Any grade	Grade 3
Patients with ≥1 transient immune complex reaction[a,b,c], *n* (%)	7 (16)	1 (2)
Patients experiencing manifestations of transient immune complex reactions[d], *n* (%)		
Arthralgia	3 (7)	1 (2)
Rash	3 (7)	0
Pain in extremity	2 (5)	0
Dizziness	1 (2)	1 (2)
Abdominal pain upper	1 (2)	1 (2)
Nausea	1 (2)	1 (2)
Myalgia	1 (2)	0
Neck pain	1 (2)	0
Rash maculo-papular	1 (2)	0
Rash papular	1 (2)	0
Headache	1 (2)	0
Pyrexia	1 (2)	0
Vasculitis	1 (2)	0

[a]Multiple occurrences of the same AE in one individual are counted once at the greatest intensity for this preferred term.
[b]Investigator text for AEs encoded using MedDRA version 24.1.
[c]Five patients received treatment for a transient immune complex reaction; treatments included betamethasone and prednisolone (one patient), paracetamol (two patients), loxoprofen (one patient), ketoprofen (two patients), naproxen (one patient), cetirizine (one patient), and topical fluocinolone (one patient).
[d]Patients can experience more than one manifestation of transient immune complexes; those who presented with multiple manifestations were included under each manifestation.

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death due to colorectal cancer, assessed as unrelated to study drug by the investigator, occurred in the crovalimab arm in the extension period.

Infections were reported in 41% ($n = 18$) of crovalimab-treated patients and 36% ($n = 15$) of eculizumab-treated patients (Supplemental Table 4); these infections were serious in 7% ($n = 3$) and 2% ($n = 1$) of patients, respectively. The serious infections that occurred in the crovalimab arm were nasopharyngitis ($n = 1$), pneumonia ($n = 1$), and urinary tract infection ($n = 1$); all considered unrelated to crovalimab by the investigator. The one patient in the eculizumab arm who

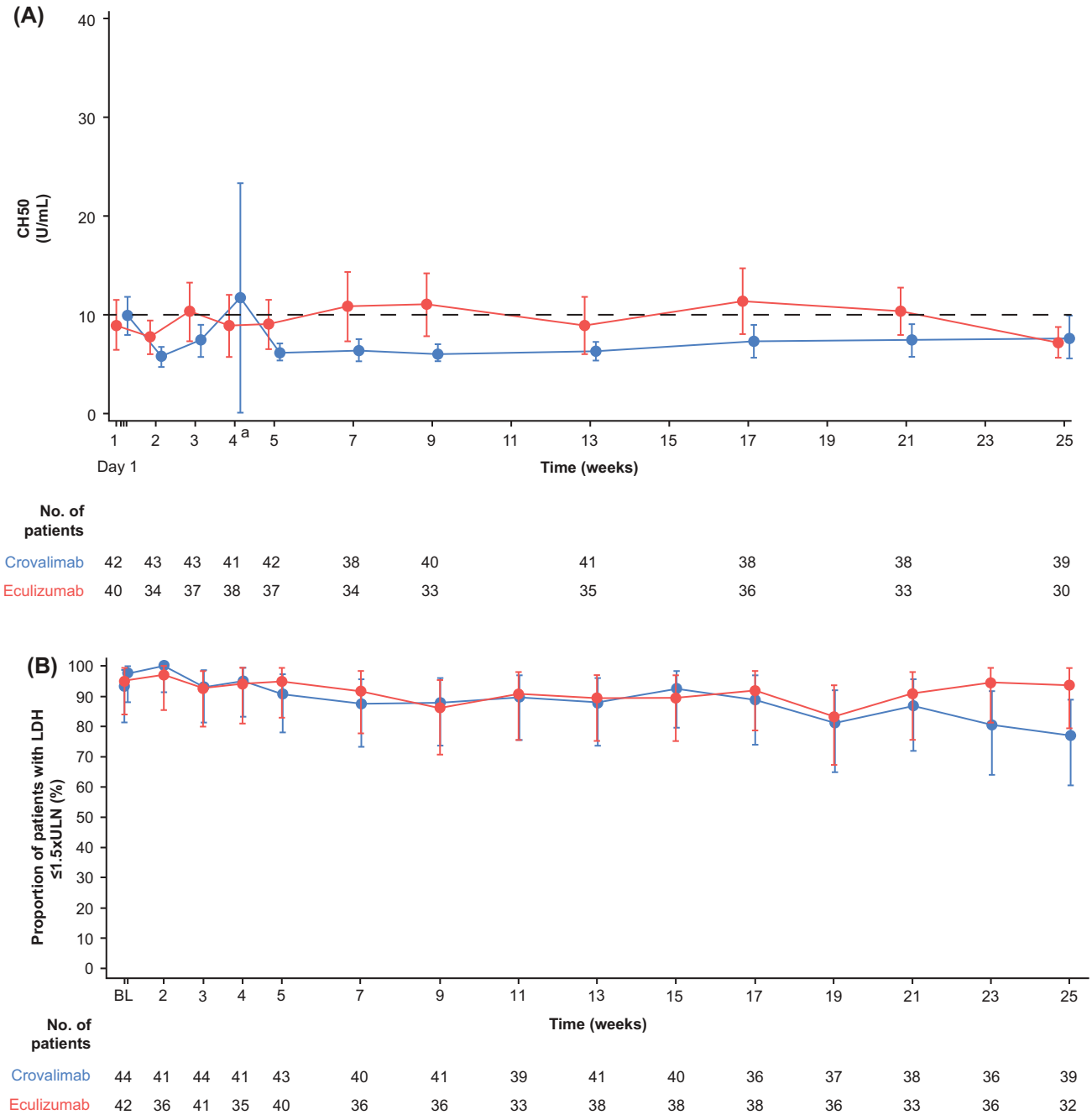


FIGURE 1 CH50 time course (measured by LIA) and proportion of patients with central LDH ≤1.5 × ULN by visit in the crovalimab and eculizumab arms from baseline to Week 25. (A) CH50 time course showing mean terminal complement activity. The dotted line represents the LLOQ for the CH50 assay (10 U/mL). CH50 concentrations <10 U/mL were set to 5 U/mL (LLOQ/2) for purposes of analysis. (B) Proportion of patients with central LDH ≤1.5 × ULN by visit from baseline to Week 25. Lines represent mean values and bars show 95% CIs. Patient numbers represent the number of patients with available CH50 or LDH data at each visit. The large error bar in the CH50 graph for crovalimab at Week 4 was due to an outlying value of CH50 that is not considered to be clinically relevant. [Color figure can be viewed at wileyonlinelibrary.com]

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reported a serious adverse event had pyelonephritis and pneumonia, both considered unrelated to eculizumab treatment. No meningococcal infections were reported.

Over the 24-week primary treatment period, the number of reported infections per 100 patient years was 135.9 (95% CI: 88.75, 199.06) in the crovalimab arm compared with 115.7 (95% CI: 71.60, 176.82) in the eculizumab arm. The number of serious infections per 100 patient years was 15.7 (95% CI: 3.23, 45.81) in the crovalimab arm compared with 11.0 (95% CI:1.33, 39.80) in the eculizumab arm.

3.3 | Pharmacokinetics and pharmacodynamics

Crovalimab concentrations were above ≈100 μg/mL (the threshold for complete terminal complement inhibition[29]) from the end of the first IV infusion in 93% of patients receiving crovalimab. Crovalimab exposure levels reached a plateau by Week 9 and then remained stable until Week 25 (Supplemental Figure 3). In crovalimab- and eculizumab-treated patients, mean CH50 baseline levels (≈10 U/mL) were maintained below or close to the lower limit of quantification (LLOQ; 10 U/mL), indicating complete inhibition of terminal complement activity (Figure 1A). Mean CH50 levels were numerically lower with crovalimab versus eculizumab. In the therapeutic exposure range, some patients in both arms experienced CH50 fluctuations up to 30 U/mL.

Mean free C5 data were consistent with CH50 results and showed a sustained inhibition of terminal complement activity in the crovalimab arm (Supplemental Figure 4). With crovalimab, total mean C5 levels decreased from 0.30 g/L at baseline and reached a plateau of 0.18 g/L at Week 4. In the eculizumab arm, mean total C5 levels were 0.28 g/L at baseline and remained stable during 24 weeks of treatment (Supplemental Figure 5).

3.4 | Exploratory efficacy

The efficacy-evaluable population included 39 and 37 patients from the crovalimab and eculizumab arms, respectively. The mean proportion of patients with hemolysis control, averaged over each visit from baseline through Week 25, was 92.9% (95% CI: 86.6, 96.4) with crovalimab versus 93.7% (95% CI: 87.3, 97.0) with eculizumab (odds ratio, 0.88; 95% CI: 0.28, 2.77; Table 3). At each visit, the proportion of patients with hemolysis control (centrally assessed LDH ≤1.5 × ULN) was generally maintained in both arms up to Week 25 (Figure 1B). Mean normalized LDH levels remained ≤1.5 × ULN in both the crovalimab and eculizumab arms throughout the primary treatment period (Supplemental Figure 6). Transfusion

TABLE 3 Exploratory efficacy outcomes from baseline through Week 25.

	Crovalimab ($n = 39$)	Eculizumab ($n = 37$)
Patients achieving hemolysis control, mean, % (95% CI)[a]	92.9 [86.6, 96.4]	93.7 [87.3, 97.0]
Odds ratio (95% CI)[b]	0.88 [0.28, 2.77]	
Proportion of patients with event, *n* (%) (95% CI)[c]		
Transfusion avoidance[d]	31 (79.5) [63.1, 90.1]	29 (78.4) [61.3, 89.6]
Weighted difference, % (95% CI)	1.8 [−16.7, 19.9]	
Breakthrough hemolysis[e]	4 (10.3) [3.3, 25.2]	5 (13.5) [5.1, 29.6]
Weighted difference, % (95% CI)	−3.5 [−19.2, 11.7]	
Hemoglobin stabilization[f]	23 (59.0) [42.2, 74.0]	26 (70.3) [52.8, 83.6]
Weighted difference, % (95% CI)	−10.8 [−30.8, 10.4]	
Adjusted mean change in FACIT-Fatigue (95% CI)[g]	1.1 [−1.5, 3.7]	−2.6 [−5.4, 0.1]
Difference in mean change, (95% CI)	3.7 [0.1, 7.4]	

Note: Only patients randomized ≥24 weeks before the clinical cutoff are included.
[a]Central LDH ≤1.5 × ULN.
[b]Odds ratio >1 favors crovalimab.
[c]Weighted differences in proportions of patients with transfusion avoidance, breakthrough hemolysis, and hemoglobin stabilization were computed using Mantel–Haenszel weights, and 95% CIs were estimated using the stratified Newcombe method.
[d]One patient in the eculizumab arm discontinued treatment before Week 25 without a transfusion and was conservatively assumed as having had a transfusion.
[e]Two patients in the eculizumab arm without a breakthrough hemolysis event discontinued treatment before Week 25 and were therefore conservatively assumed as having a breakthrough hemolysis event.
[f]One patient in the eculizumab arm discontinued treatment before Week 25 and was conservatively assumed as not having stabilized hemoglobin.
[g]Mean change was calculated as Week 25 versus baseline.

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avoidance was achieved by 31 of 39 patients (79.5%, 95% CI: 63.1, 90.1) receiving crovalimab and 29 of 37 patients (78.4%, 95% CI: 61.3, 89.6) receiving eculizumab (Table 3). The mean number of pRBC units transfused from baseline to Week 25 was 4.75 (95% CI: 2.53, 6.97) in the eight patients who required a transfusion in the crovalimab arm and 10.00 (95% CI: 7.80, 12.20) in the seven patients who required a transfusion in the eculizumab arm. Of note, one additional patient in the eculizumab arm had discontinued treatment before Week 25 without a transfusion and therefore was conservatively assumed to have had a transfusion.

Four of 39 patients (10.3%, 95% CI: 3.3, 25.2) receiving crovalimab and 5 of 37 (13.5%, 95% CI: 5.1, 29.6) receiving eculizumab experienced a breakthrough hemolysis event. Based on pharmacokinetic/pharmacodynamic analysis, no breakthrough hemolysis events for crovalimab were attributed to an inadequate/inappropriate dosing regimen, and as expected, the majority of breakthrough hemolysis events were due to a complement-activating condition. Management of breakthrough hemolysis events was determined by the investigator, including pRBC transfusions and an IV crovalimab rescue dose if applicable per protocol.

Hemoglobin stabilization was achieved in 23 of 39 patients (59.0%, 95% CI: 42.2, 74.0) treated with crovalimab and 26 of 37 (70.3%, 95% CI: 52.8, 83.6) treated with eculizumab (Table 3).

No patients in the crovalimab arm experienced a major adverse vascular event from baseline to Week 25. One patient in the eculizumab arm, without a history of a major adverse vascular event, experienced a transient ischemic attack that resolved with treatment and, in the investigator's opinion, was unrelated to eculizumab.

Adjusted mean change from baseline to Week 25 in FACIT-Fatigue score was 1.1 (95% CI: −1.5, 3.7) with crovalimab, and −2.6 (95% CI: −5.4, 0.1) with eculizumab; adjusted mean difference between arms was 3.7 (95% CI: 0.1, 7.4; Table 3).

3.5 | Patient preference for crovalimab versus eculizumab

Overall, 33 of 39 patients (85%) in the randomized crovalimab arm preferred crovalimab over eculizumab after 17 weeks of treatment (Supplemental Table 5). The top three reasons selected from the Patient Preference Questionnaire for crovalimab preference were "the way treatment was given was easier", "time to administer treatment was shorter", and "fewer hospital visits associated with treatment".

3.6 | Crovalimab self-administration

Between Weeks 9 and 25, most subcutaneous drug administrations were performed by a healthcare professional (range, 84.2%–88.4%), whereas subcutaneous administrations conducted by the patient or caregiver ranged between 11.6% and 15.8% (Supplemental Figure 7). After Week 25, administrations by the patient or their caregiver tended to increase over time. No medication errors specifically due to self-administration were reported up to clinical cutoff.

4 | DISCUSSION

In COMMODORE 1, the safety, pharmacokinetics, pharmacodynamics, and exploratory efficacy of crovalimab versus eculizumab were assessed in C5 inhibitor-experienced patients with PNH. Baseline characteristics were generally well balanced across arms and represented the C5 inhibitor-experienced population intended to be enrolled.[13] Despite not being powered for statistical testing of efficacy endpoints, this study provides valuable randomized data from a large cohort of C5 inhibitor-experienced patients, allowing for the comparative evaluation of safety and exploratory efficacy in patients who switched from eculizumab to crovalimab versus those who continued on eculizumab.

The safety profile of crovalimab in C5 inhibitor-experienced patients with PNH in COMMODORE 1 was consistent with that seen in C5 inhibitor-naive patients in other crovalimab trials,[23–25] except for the anticipated risk of transient immune complex reactions.

The transient immune complex reactions seen in this study have been previously described,[28] and were expected to occur in a subset of patients switching between C5 inhibitors that bind to different C5 epitopes, as a result of transient immune complex formation (eculizumab/ravulizumab-C5-crovalimab motifs).[21] In COMMODORE 1, consistent with previous reports,[21,28] these reactions manifested clinically as rashes and/or arthralgia in most patients. Management typically involves symptomatic treatment and/or corticosteroid therapy for more severe cases. Currently, no baseline biomarkers or demographic variables have been identified or other analyses performed that can identify patients at higher risk of transient immune complex reactions. In this study, most transient immune complex reactions were mild or moderate and self-limiting, with no life-threatening or fatal events reported, and resolved with no change in crovalimab treatment.

Rates of all-grade and serious AEs were numerically higher in the crovalimab versus eculizumab arm of COMMODORE 1. However, given the design of the study, some noteworthy points may account for this observed difference. Patients randomized to receive crovalimab were initiating a novel anti-complement therapy, unlike patients randomized to the eculizumab arm who continued an already established and tolerated treatment. The higher percentages of all-grade AEs and treatment-related AEs were also driven by a combination of risks unique to the crovalimab arm. For example, the switch from eculizumab to crovalimab could lead to transient immune complex reactions (16% with crovalimab vs. not applicable with eculizumab), that were expected only in the crovalimab arm due to the formation of transient immune complexes between two molecules and C5. Additionally, injection site reactions (9% vs. not applicable with eculizumab) were expected only in the crovalimab arm due to subcutaneous administration. Infusion-related reactions (related to a single IV loading dose) also occurred only in the crovalimab arm (14% vs. 0 with eculizumab), likely due to the steady receipt of eculizumab for

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≥24 weeks before study enrollment; new events were not anticipated with continued eculizumab dosing after enrollment. Furthermore, the higher proportion of Grade ≥3 AEs reported in the crovalimab arm of COMMODORE 1 was not driven by known risks associated with crovalimab, and most events occurred in single patients across various preferred terms with no pattern indicative of a safety concern associated with crovalimab.

These conclusions are supported by data from COMMODORE 2 in C5 inhibitor-naive patients.[24] Contrary to COMMODORE 1 in C5 inhibitor-experienced patients, the absence of pre-study exposure to anti-complement therapy in COMMODORE 2 allows for a more equal comparison of AE rates between crovalimab and eculizumab arms.[24] In COMMODORE 2, rates of all-grade AEs (78% with crovalimab vs.S 80% with eculizumab), grade ≥3 AEs (18% vs. 25%), treatment-related AEs (33% vs. 35%), and infusion-related reactions (16% vs. 13%) were similar between the crovalimab and eculizumab arms,[24] and additionally, similar to those for the crovalimab arm in COMMODORE 1.

Furthermore, in this COMMODORE 1 study, the numerically higher percentage of patients who developed infections in the crovalimab versus eculizumab arm was driven by only three patients and is therefore also not likely to be clinically meaningful. Additionally, although the patient-year adjusted infection rates also showed a numerically higher rate in the crovalimab arm, they did not indicate a clinically relevant increase in the risk of infection with crovalimab, with overlapping 95% CIs seen between arms. Additionally, in C5 inhibitor-naive patients in the COMMODORE 2 study, rates of infections (24% vs. 36%) and serious infections (3% vs. 7%) were numerically lower with crovalimab versus eculizumab.[24] Taken together, data from COMMODORE 1 and COMMODORE 2 indicate that the safety profile of crovalimab in patients with PNH is comparable to that of eculizumab. No new safety concerns were identified for crovalimab.

Pharmacokinetic and pharmacodynamic profiles showed complete and sustained inhibition of terminal complement activity in patients who switched from eculizumab to crovalimab, evidenced by crovalimab concentrations that were generally maintained above 100 μg/mL (the threshold for complete terminal complement inhibition[29]), and low levels of CH50 and serum free C5. Although mean CH50 levels were numerically lower in the crovalimab arm, this difference was not meaningful, likely due to levels being close to or below the LLOQ in both groups. CH50 fluctuations up to 30 U/mL observed in some patients in both arms were not considered clinically significant, as they were not associated with an impact on clinical response, based on the LDH efficacy parameter. Mean levels of total C5 were numerically lower with crovalimab likely due to crovalimab's recycling technology. Crovalimab is recycled as a free monoclonal antibody, leading to a rapid clearance of C5 in plasma,[20] thus resulting in a lower plateau of total C5 concentration than with eculizumab.[21]

Complete terminal complement inhibition was achieved using a model-optimized dosing regimen of crovalimab that reduced the formation of large transient immune complexes, allowing for faster clearance of these complexes and increasing the likelihood that complete complement inhibition could be maintained throughout crovalimab treatment.[23,28]

Exploratory efficacy results during the 24-week primary treatment period further indicated maintenance of disease control. Patients who switched from eculizumab to crovalimab showed similar results to those who continued eculizumab for hemolysis control, transfusion avoidance, breakthrough hemolysis, and self-reported fatigue. The proportion of patients who achieved hemoglobin stabilization was numerically higher in the eculizumab arm; however, this was only driven by a difference of three patients between the arms. In both arms, most hemoglobin decreases without a concurrent transfusion were singular decreases in the context of a complement-activating condition, with or without a reported breakthrough hemolysis event per protocol. Moreover, this difference across arms was not seen in the transfusion avoidance endpoint. In general, efficacy in the eculizumab arm of this study was consistent with the known treatment effects of eculizumab.[11–13]

Although eculizumab treatment has improved disease control, survival outcomes, and self-reported fatigue in patients with PNH, the requirement for every-2-week IV dosing (typically in a supervised healthcare setting, with home-based therapy available in some countries) represents a large treatment burden and likely negatively affects patients' quality of life.[30,31] Crovalimab, which allows for every-4-weeks subcutaneous dosing, with the ability to self-administer, may reduce treatment burden for patients and enable patients and physicians more freedom in managing PNH, while maintaining control of the disease and patient-reported fatigue. Additionally, most patients in this study who switched to crovalimab expressed a preference for crovalimab over eculizumab.

Overall, the COMMODORE 1 study showed that crovalimab was well tolerated, and maintained disease control with sustained and complete terminal complement inhibition in patients switching from eculizumab to crovalimab. These safety and efficacy data support the overall favorable benefit–risk profile of crovalimab seen in the COMMODORE 2 trial, where crovalimab was non-inferior compared with eculizumab in treatment-naive patients with PNH.[24] With comparable safety and efficacy versus eculizumab in patients with PNH, crovalimab is a new C5 inhibitor treatment option that is potentially less burdensome than existing therapies in the context of this chronic lifelong disease.

AUTHOR CONTRIBUTIONS

Conception and design of the study: B.G., A.K., S.S., M.U. Recruited patients and/or collected data: P.S., D.V.C., J.S.K., E.N., M.N.Y., W.B., D.B., V.G., M.H., Y.J.L., C.B.L., J.P., Y.U., Z.N., A.G.K. Analyzed and interpreted the data: P.S., J.S.K., J.P., S.B., B.G., A.K., H.P., S.S., M.U., J.E., A.G.K. Contributed to the manuscript and provided final approval: All authors.

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CONFLICT OF INTEREST STATEMENT

P.S. declares consultancy for AbbVie, F. Hoffmann-La Roche Ltd, Alexion, Janssen, Pfizer, Amgen, BioCryst and AstraZeneca; research funding from Alnylam and Pfizer; speaker's bureau participation for Novartis, Pfizer, and Alexion. D.V.C. declares consultancy for Takeda, Novartis, Janssen, Astra Zeneca, MSD, Alexion and Zodiac; speaker's bureau participation for Takeda, Novartis, Janssen, AbbVie, Astra Zeneca, and Alexion. J.S.K. declares research funding from Alexion and F. Hoffmann-La Roche Ltd. E.N. declares consultancy for Novartis; speaker's bureau participation for Novartis and Vertex. M.N.Y. declares consultancy from Alexion, AstraZeneca Rare Disease, Pfizer, Sanofi, Sobi, Adeka and Pierre Fabre. W.B. declares consultancy from Agios, Alexion, Biocryst, Incyte, Momenta, Novartis, Roche, Sanofi, and Sobi; research support from Alexion. D.B. declares no conflicts of interest. V.G. declares honoraria from Alexion and Novartis. M.H. declares consultancy for Alexion, Sobi and AstraZeneca Rare Disease; honoraria from Sobi and Alexion. Y.J.L. declares no conflicts of interest. C.B.L. declares consultancy for Alexion; honoraria from Alexion, and is a member of an advisory board for Alexion. J.P. declares payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Alexion, Amgen, Apellis, AstraZeneca, Blueprint Medicines, Bristol Myers Squibb, Boehringer Ingelheim, Gilead, MSD, Novartis, Pfizer, F. Hoffmann La-Roche Ltd, Sanofi, and Sobi; support for attending meetings and/or travel from Alexion, Blueprint Medicines, Boehringer Ingelheim, Novartis, Pfizer, F. Hoffmann-La Roche Ltd, and Sobi; participation on a data safety monitoring board or advisory board for Alexion, Amgen, Apellis, AstraZeneca, Blueprint Medicines, Bristol Myers Squibb, Boehringer Ingelheim, Gilead, MSD, Novartis, Pfizer, F. Hoffmann-La Roche Ltd, Sanofi, and Sobi; leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid for www.lichterzellen.de; receipt of equipment, materials, drugs, medical writing, gifts or other services from Apellis, Blueprint Medicines, Novartis, F. Hoffmann-La Roche Ltd, and Sobi. Y.U. declares consultancy for Alexion, Asahi Kasei, Chugai Pharmaceutical Co., Ltd, Novartis, Sanofi, Sobi, and Janssen; research funding from Chugai Pharmaceutical Co., Ltd; honoraria from Alexion, Sanofi, Novartis and Sobi; speaker's bureau participation for Incyte Biosciences; membership on a board or advisory committee for Alexion, Novartis and Sanofi. S.B. and M.U. declare employment at F. Hoffmann-La Roche Ltd. B.G., H.P., and S.S. declare employment at Genentech, Inc. A.K. declares employment and stock ownership at F. Hoffmann-La Roche Ltd. J.E. declares consultancy for Jazz Pharmaceuticals and F. Hoffmann-La Roche Ltd; speaker's bureau involvement for Jazz Pharmaceuticals and Astellas. Z.N. is a member of an entity's board of directors or advisory committee for Janssen, Novartis, Takeda, AbbVie, and F. Hoffmann-La Roche Ltd. A.G.K. declares honoraria from Agios, Alexion, AstraZeneca Rare Disease; Amgen; Celgene/BMS; Novartis; and Ra Pharma/UCB; is on the board of directors or is an advisory board member for Agios, Alexion, AstraZeneca Rare Disease; Amgen; Celgene/BMS; Geron; Novartis; Roche; and Ra Pharma; and has received consulting fees from Achillion; Agios Pharmaceuticals; Akari Therapeutics; Alexion, AstraZeneca Rare Disease; Biocryst; Celgene/BMS; Novo Nordisk; Janssen Pharmaceuticals; Roche; Samsung; and Novartis.

DATA AVAILABILITY STATEMENT

For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see: https://go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification.

PATIENT CONSENT STATEMENT

All patients provided written informed consent to participate in the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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