Terminal complement inhibition and control of hemolysis in patients with paroxysmal nocturnal hemoglobinuria who switched from high-dose eculizumab to ravulizumab: a phase IV, single-arm clinical trial

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, chronic, hematologic disorder characterized by uncontrolled terminal complement activation, intravascular hemolysis, and potentially life-threatening thromboses, leading to early mortality.[1,2] The complement component 5 (C5) inhibitor eculizumab and its analog ravulizumab (the current standard of care) are approved treatments for PNH. Both treatments inhibit intravascular hemolysis, reduce the incidence of thrombosis, and are associated with improvements in anemia, transfusion dependence, quality of life, and survival when administered at their respective 2-week (eculizumab) and 8-week (ravulizumab) dosing intervals.[3-9] Some patients treated with eculizumab at the approved fixed-dose regimen of 900 mg every 2 weeks (Q2W) experience intravascular hemolysis toward the end of the fixed-dosing interval.[6,10] This can be managed by shortening the dosing interval, which may increase the treatment burden for both patients and healthcare providers,[7,11,12] or by using a higher than approved dose.[6,10]

Ravulizumab offers immediate, complete, and sustained inhibition of complement-mediated intravascular hemolysis at 8-week dosing intervals.[7,11,12] In clinical trials, weight-based doses of ravulizumab demonstrated non-inferiority and a comparable safety profile to approved fixed-dose eculizumab in patients with PNH,[11,12] with durable efficacy and tolerance for up to 4 years following a switch from fixed-dose eculizumab.[7] Although a single case describing treatment switch from high-dose eculizumab to standard weight-based ravulizumab has been reported,[13] there are currently no clinical trial data reporting the feasibility and safety of this switch in patients with PNH.

Here, we report findings from study 401 (NCT04320602), a phase IV, single-arm, two-center trial conducted in the UK between April 2021 and December 2022 that was designed to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of switching treatment from high-dose intravenous eculizumab (1,200 mg Q2W) to weight-based intravenous ravulizumab Q8W in patients with PNH. Included patients were aged ≥18 years with a documented diagnosis of PNH, who had received high-dose intravenous eculizumab for ≥3 months prior to screening and had lactate dehydrogenase (LDH) levels ≤2 × upper limit of normal (ULN; 281.0 U/L, central laboratory assessment) at screening. All patients had received meningococcal vaccines A/C/Y/W-135 conjugate and B within 3 years prior to the start of the study. Key exclusion criteria were body weight <40 kg at screening, history of major adverse vascular events within 6 months prior to enrollment, bone marrow transplantation, malignancy within 5 years prior to enrollment, platelet count <30×10^9/L, and neutrophil count <0.5×10^9/L. Ethical approval for this study was received from Yorkshire and the Humber – Leeds East Research Ethics Committee (reference: 20/YH/0105). Patients consented to participation in the study and could withdraw at any time.

During the 3-month pre-baseline period, patients continued to receive stable doses of eculizumab 1,200 mg Q2W; LDH, free C5, and hemoglobin levels were measured on day −85 (LDH and hemoglobin only), day −57, and day −15, immediately before eculizumab infusion. On day 1 (baseline), patients switched treatment to ravulizumab, receiving an initial loading dose (patients weighing ≥40-<60 kg: 2,400 mg; patients weighing ≥60-<100 kg: 2,700 mg; patients weighing ≥100 kg: 3,000 mg), followed by a maintenance dose on day 15 and Q8W thereafter (patients weighing ≥40-<60 kg: 3,000 mg; patients weighing ≥60-<100 kg: 3,300 mg; patients weighing ≥100 kg: 3,600 mg) up to day 351 (end of study).

The primary endpoint was the proportion of patients who experienced free C5-associated intravascular hemolysis (also called breakthrough hemolysis). Breakthrough hemolysis was defined as the presence of at least one new or worsening PNH symptom or sign of intravascular hemolysis, with LDH ≥2×ULN and free C5 concentration ≥0.5 μg/mL. Secondary endpoints included LDH percentage change, proportion of patients who received a transfusion, and proportion of patients with stabilized hemoglobin (avoidance of a ≥2 g/dL decrease in hemoglobin concentration in the absence of transfusion). Safety endpoints included the proportion of patients with treatment-emergent adverse events and serious treatment-emergent adverse events, and proportion of patients who developed antidrug antibodies to ravulizumab.

Overall, 18 patients were screened and enrolled into the study, all of whom completed study treatment up to day 351. The baseline characteristics of the study population are presented in Table 1. Two patients had low red blood cell clone sizes (5%) although their monocyte clone size was 24% and 71%, respectively.

Per-patient laboratory values are available in *Online Supplementary Table S1*. Throughout the study period, individual serum free C5 concentrations were <0.5 μg/mL in

all participants (Figure 1A). One instance of breakthrough hemolysis was reported in a patient on day 61 (symptoms: abdominal pain, fatigue, macroscopic hemoglobinuria, and shortness of breath), which was considered related to vaccinations for COVID-19 and influenza received the day prior to the event. At the study timepoint prior to the breakthrough hemolysis event (day 15), this patient's LDH level was ≤1×ULN, free C5 concentration was 0.0192 μg/mL, and hemoglobin level was 12.0 g/dL. At 4 days after the event, the local laboratory-reported LDH level was 2×ULN, while the free C5 concentration was 0.11 μg/mL and the hemoglobin level was 11.5 g/dL. The patient continued ravulizumab treatment without altering the dose or dosing interval, and on day 127 the LDH level was ≤1×ULN.

Central laboratory LDH levels were ≤1.5×ULN for all patients (Figure 1B). Median hemoglobin levels ranged from 10.6 g/dL to 11.3 g/dL during the study (*Online Supplementary Figure S1, Online Supplementary Table S1*), with 11 patients maintaining stable hemoglobin levels (avoidance of a ≥2 g/dL decrease in hemoglobin in the absence of transfusion) up to day 351. Six patients (33.3%) required a total of ten transfusions during the ravulizumab treatment period. Of these patients, two had received transfusions within 12 months prior to enrollment (one of whom required a transfusion during the pre-baseline period [day –14]). Hemoglobin levels prior to transfusion ranged from 4.6 g/dL to 8.0 g/dL; investigator-recorded reasons for transfusion other than low hemoglobin (N=7) included COVID-19 infection (N=1), chest infection (N=1), and extravascular hemolysis (N=1); see *Online Supplementary Figure S2* for details.

In total, 16 patients (88.9%) reported 63 treatment-emergent adverse events during the ravulizumab treatment period, which were predominantly mild (27.8%) or moderate (44.4%) in severity; none led to death or study withdrawal. Five patients (27.8%) experienced treatment-emergent adverse events considered to be treatment-related (9 events, comprising fatigue, non-cardiac chest pain, headache, asthenia, and nail ridging) (Table 2). Serious treatment-emergent adverse events were reported in three patients (16.7%; comprising pneumonia, urinary tract infection, retinal hemorrhage, pyrexia, and headache), none of which was deemed related to treatment. One extravascular hemolysis event was reported as an explanation for why a patient required transfusion; it is possible that other patients experienced some degree of extravascular hemolysis which was not reported as an adverse event (hemoglobin and reticulocyte count data for individual patients are shown in *Online Supplementary Table S1*). There were no major adverse vascular events, meningococcal infections, or clinical signs of anti-drug antibodies to ravulizumab. Following study completion, one subclavian vein thrombosis event was reported on day 461; no known complement-activating events were identified in this patient.

This clinical trial was the first to investigate the feasibility of switching treatment from high-dose eculizumab to weight-based ravulizumab in patients with PNH who required a higher than approved dose of eculizumab for

Table 1. Patients' baseline demographics and clinical characteristics (N=18).

Characteristics	Total N=18
Age in years, median (range)[a]	58.0 (22-73)
Age at PNH diagnosis in years, median (range)	41.0 (18-62)
Male, N (%)	12 (66.7)
Weight, kg, median (range)[b]	81.70 (49.5-114.0)
Weight category, N (%)[b]	
≥40 kg to <60 kg	2 (11.1)
≥60 kg to <100 kg	13 (72.2)
≥100 kg	3 (16.7)
Total RBC PNH clone size at screening, %, median (range)	85.5 (5-99)
Granulocyte clone size at screening, %, median (range)	98.5 (7-100)
Monocyte clone size at screening, %, median (range)	98.0 (24-99)
LDH level, U/L, median (range)[c]	230.05 (158.5-343.0)
LDH ≤1×ULN, N (%)[c,d]	17 (94.4)
Hb concentration, g/dL, median (range)[b]	11.1 (7.8-14.1)
Free C5 concentration, μg/mL, median (range)[b]	0.0092 (0.0092-0.0483)
Received pRBC/transfusions during 3-month pre-baseline period, N (%)	1 (5.6)
History of aplastic anemia, N (%)	7 (38.9)
History of any conditions associated with MAVE, N (%)[e]	8 (44.4)
Hepatic/portal vein thrombosis (Budd-Chiari syndrome)	3 (16.7)
Thrombophlebitis/deep vein thrombosis	2 (11.1)
Mesenteric/visceral arterial thrombosis or infarction	1 (5.6)
Myocardial infarction	1 (5.6)
Cerebral vein thrombosis	1 (5.6)
Transient ischemic attack	1 (5.6)
Other[f]	5 (27.8)

[a]At the time of informed consent. [b]Considered the most recent value captured prior to the first ravulizumab infusion. Free C5 concentration <0.00915 μg/mL was utilized as the lower limit of quantification. [c]Calculated using the average of all screening assessments (day –85, day –57, and day –29) captured prior to the first ravulizumab infusion. [d]Upper limit of normal of lactate dehydrogenase level: 281.0 U/L. [e]N is the number of participants who had at least one event in the category; three patients had findings in more than one category. [f]Additional findings reported by investigator: extravascular hemolysis (N=1), minor myocardial damage (N=1), leg swelling (suspected deep vein thrombosis; N=1), subclinical pulmonary embolism (N=1), and thrombosis (chest; N=1). PNH: paroxysmal nocturnal hemoglobinuria; RBC: red blood cell; LDH: lactate dehydrogenase; ULN: upper limit of normal; Hb: hemoglobin; C5: complement component 5; pRBC: packed red blood cells; MAVE: major adverse vascular event.

complete C5 inhibition over the 14-day dosing interval. Switching treatment to weight-based ravulizumab Q8W maintained complete and sustained inhibition of terminal complement activity and complement-mediated intravascular hemolysis. Free C5 concentrations were <0.5 μg/mL at all study timepoints, indicating appropriate suppression of C5 activity, thereby satisfying the primary outcome for this study. Hemoglobin levels were also well controlled,

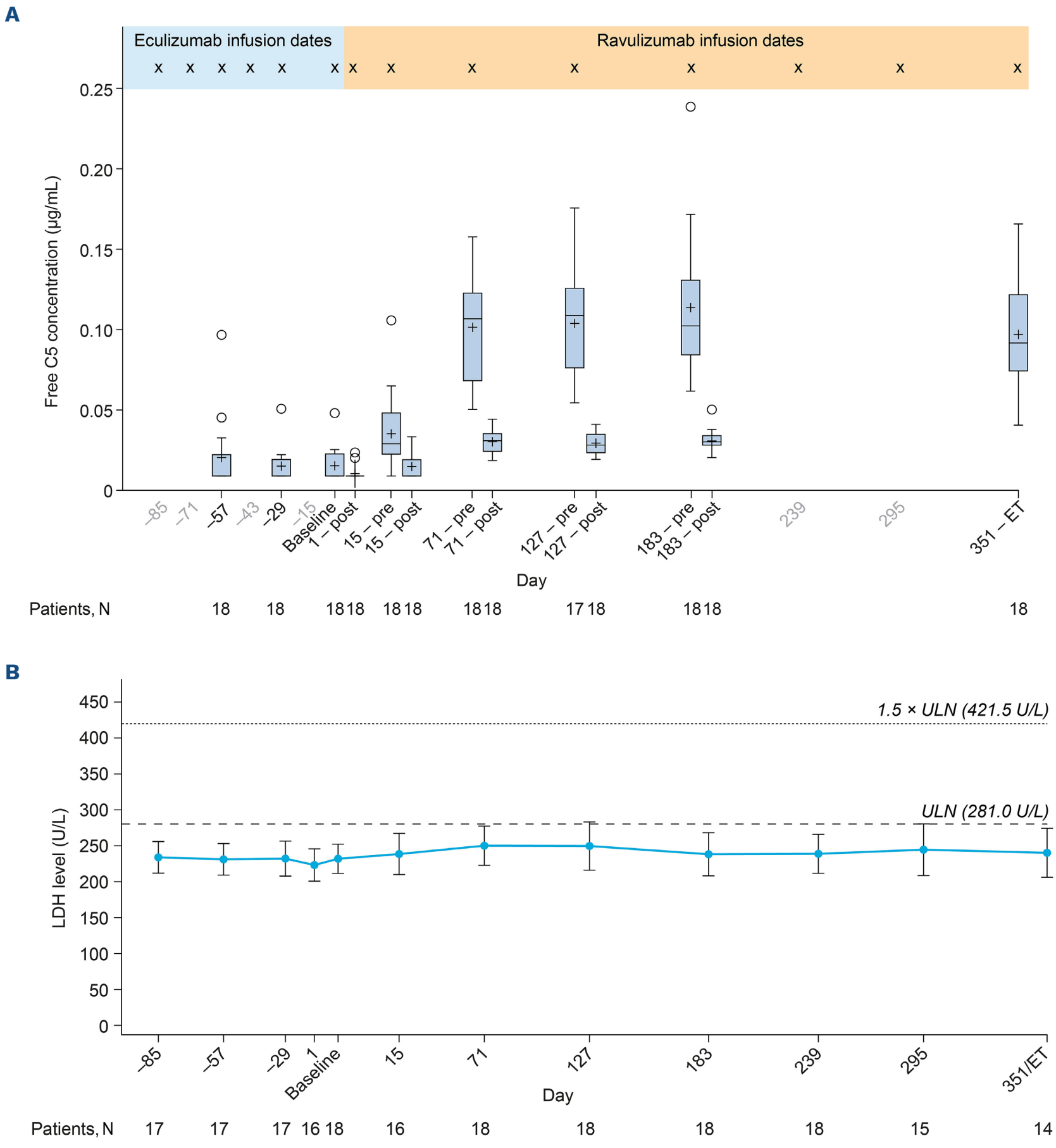

Figure 1. Complement component 5 concentration and lactate dehydrogenase level. (A) Free C5 concentration and (B) mean (95% confidence interval) lactate dehydrogenase level. A free C5 level of <0.5 μg/mL indicates effective suppression of C5. Free C5 concentration <0.00915 μg/mL was utilized as the lower limit of quantification. For box and whisker plots, a cross (+) indicates the arithmetic mean, a horizontal line indicates the median, upper and lower lines of boxes indicate 1st and 3rd quartiles (25th and 75th percentiles), whiskers represent fences of 1.5 × interquartile range (IQR) or minimum/maximum range if <1.5 × IQR and circles (o) indicate outliers. C5: complement component 5; Baseline: the last non-missing value prior to the first study drug administration; post: after ravulizumab infusion; pre: before ravulizumab infusion; ET: end of trial; LDH: lactate dehydrogenase; ULN: upper limit of normal.

with the majority of patients avoiding transfusion during the study. Therefore, despite needing a higher dose of eculizumab, approved weight-based dosing of ravulizumab was sufficient for PNH disease control in these patients, and there was no need to shorten the 8-week dosing interval.

No new ravulizumab-associated safety signals were identified and adverse events were comparable to those previously reported in adults with PNH.[7,11,12] Importantly, there were no meningococcal infections or major adverse vascular events, and no treatment-emergent adverse events that led to death or study withdrawal. The subclavian vein thrombosis reported after the study occurred in a patient whose weight was at the upper limit of the 60–100 kg weight range for the patient's ravulizumab dose, suggesting that a higher weight-based dose of ravulizumab may have been required. However, as the patient had sufficient disease control during the study period, further investigation is required.

Over the treatment period, 12/18 patients (66.7%) avoided transfusion. In previous trials of ravulizumab in patients with PNH, transfusion avoidance levels of 76.6% and 86.5% were reported following 1 year of treatment;[8,9] the lower proportion in this study may be due to the smaller sample size, the shorter follow-up, and differences in the patient populations.[8,9]

The main limitation of this study is the small sample size, which precludes formal statistical comparisons; this was to be expected given that this study was based on a subpopulation of patients with a rare disease receiving a dose above the approved fixed-dose regimen. In addition, the study recruited patients from two referral centers in a single country; consequently, the findings should be interpreted with caution and may not be generalizable to the wider PNH population. Finally, only patients receiving eculizumab 1,200 mg Q2W were included in the study, so findings may not be applicable to the small proportion of patients requiring even higher doses of eculizumab.

In summary, switching treatment from high-dose intravenous eculizumab (1,200 mg Q2W) to standard, weight-based intravenous ravulizumab resulted in minimal changes in laboratory measures at an improved dosing interval, with no new safety signals reported. Our findings support the use of weight-based ravulizumab as a suitable and well-tolerated alternative to eculizumab, even for patients who have experienced pharmacokinetic breakthrough hemolysis during standard-dose eculizumab treatment.

Table 2. Summary of treatment-emergent adverse events in patients with paroxysmal nocturnal hemoglobinuria who switched treatment from high-dose eculizumab to weight-based ravulizumab (N=18).

Adverse events	Total, N=18	
	N (%)	N of events
Any TEAE	16 (88.9)	63
Any serious TEAE	3 (16.7)	5
Infections and infestations	2 (11.1)	2
Pneumonia	1 (5.6)	1
Urinary tract infection	1 (5.6)	1
Eye disorders	1 (5.6)	1
Retinal hemorrhage	1 (5.6)	1
General disorders and ASC	1 (5.6)	1
Pyrexia	1 (5.6)	1
Nervous system disorders	1 (5.6)	1
Headache	1 (5.6)	1
Any TEAE leading to death	0	-
Any TEAE leading to study withdrawal	0	-
TEAE by maximum CTCAE grade		
Grade 1: mild	5 (27.8)	-
Grade 2: moderate	8 (44.4)	-
Grade 3: severe	3 (16.7)	-
Grade 4: life-threatening	0	-
Grade 5: fatal	0	-
TEAE considered to be a MAVE	0	-
Any TEAE related to study drug	5 (27.8)	9
General disorders and ASC	4 (22.2)	6
Fatigue	3 (16.7)	3
Non-cardiac chest pain	2 (11.1)	2
Asthenia	1 (5.6)	1
Nervous system disorders	2 (11.1)	2
Headache	2 (11.1)	2
Skin and subcutaneous tissue disorders	1 (5.6)	1
Nail ridging	1 (5.6)	1

TEAE: treatment-emergent adverse event; ASC: administration site conditions; CTCAE: Common Terminology Criteria for Adverse Events; MAVE: major adverse vascular event.

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Contributions

MG, SG, RJK, TM, PM, RT, and AGK recruited patients; collected, analyzed, and interpreted the data; contributed to the manuscript; and approved the final version. EH, DJ, MO, and JY developed the protocol, analyzed and interpreted the data, contributed to the manuscript, and approved the final version.

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Data-sharing statement

Alexion, AstraZeneca Rare Disease will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods such as data de-identification, pseudonymization, or anonymization (as required by applicable law), and if such disclosure was included in the relevant study informed consent form or similar documentation. Qualified academic investigators may request participant-level clinical data and supporting documents (statistical analysis plan and protocol) pertaining to Alexion-sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy at *https://www.alexionclinicaltrialtransparency.com/data-requests/*.

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