



Phase 3 Study of Subcutaneous Versus Intravenous Ravulizumab in Eculizumab-Experienced Adult Patients with PNH: Primary Analysis and 1-Year Follow-Up

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ABSTRACT

Introduction: This study compared the pharmacokinetics (PK) of the ravulizumab on-body delivery system for subcutaneous (SUBQ) administration with intravenous (IV) ravulizumab in eculizumab-experienced patients with paroxysmal nocturnal hemoglobinuria (PNH).

Methods: Patients with PNH received SUBQ ravulizumab ($n = 90$) or IV ravulizumab ($n = 46$) during the 10-week randomized treatment period; all patients then received SUBQ ravulizumab during an extension period (< 172 weeks; data cutoff 1 year). Primary endpoint was day 71 serum ravulizumab trough

concentration (C_{trough}). Secondary endpoints were ravulizumab C_{trough} and free C5 over time. Efficacy endpoints included change in lactate dehydrogenase (LDH), breakthrough hemolysis (BTH), transfusion avoidance, stabilized hemoglobin, and Treatment Administration Satisfaction Questionnaire (TASQ) score. Safety, including adverse events (AEs) and adverse device effects (ADEs), was assessed until data cutoff.

Results: SUBQ ravulizumab demonstrated PK non-inferiority with IV ravulizumab (day 71 SUBQ/IV geometric least-squares means ratio 1.257 [90% confidence interval 1.160–1.361; $p < 0.0001$]). Through 1 year of SUBQ administration, ravulizumab C_{trough} values were > 175 $\mu\text{g/mL}$ (PK threshold) and free C5 < 0.5 $\mu\text{g/mL}$ (PD threshold). Efficacy endpoints remained stable: mean (standard devia-

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tion, SD) LDH percentage change was 0.9% (20.5%); BTH events, 5/128 patients (3.9%); 83.6% achieved transfusion avoidance; 79.7% achieved stabilized hemoglobin. Total TASQ score showed improved satisfaction with SUBQ ravulizumab compared with IV eculizumab (mean [SD] change at SUBQ day 351, -69.3 [80.1]). The most common AEs during SUBQ treatment (excluding ADEs) were headache (14.1%), COVID-19 (14.1%), and pyrexia (10.9%); the most common ADE unrelated to a device product issue was injection site reaction (4.7%). Although many patients had ≥ 1 device issue-related ADE, full SUBQ dose administration was achieved in 99.9% of attempts.

Conclusions: SUBQ ravulizumab provides an additional treatment choice for patients with PNH. Patients may switch to SUBQ ravulizumab from IV eculizumab or ravulizumab without loss of efficacy.

Trial Registration: NCT03748823.

PLAIN LANGUAGE SUMMARY

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare blood disorder characterized by the destruction of red blood cells (hemolysis) within blood vessels. In addition to hemolysis, patients with PNH are susceptible to life-threatening blood clots (thromboses). Eculizumab and ravulizumab are types of treatments for PNH, called C5 inhibitors. In the blood, these treatments bind to C5 protein and prevent the destruction of red blood cells, reducing the symptoms and complications of PNH. Both treatments are approved for use via intravenous (through the vein) administration. Ravulizumab is also approved in the USA for use via subcutaneous (under the skin) administration. This study compared subcutaneous ravulizumab with intravenous ravulizumab in patients with PNH who had previously been treated with eculizumab. During the initial treatment period of 71 days, 90 patients received subcutaneous ravulizumab and 46 received intravenous ravulizumab. Following this period, all patients received subcutaneous ravulizumab. At day 71, the amount of ravulizumab in the blood of

patients taking subcutaneous ravulizumab was no less than in patients taking intravenous ravulizumab and was maintained over 1 year of treatment. Efficacy measures (how well it works) remained stable in patients taking subcutaneous ravulizumab for 1 year and side effects were comparable with those of intravenous ravulizumab. Patients reported more satisfaction with subcutaneous ravulizumab than intravenous eculizumab, as assessed by the Treatment Administration Satisfaction Questionnaire. This study showed that patients with PNH can switch from intravenous eculizumab or ravulizumab to subcutaneous ravulizumab without loss of efficacy. Subcutaneous ravulizumab provides an additional treatment choice for patients with PNH.

Keywords: Non-inferiority; Paroxysmal nocturnal hemoglobinuria; Quality of life; Ravulizumab; Subcutaneous

Key Summary Points

Why carry out this study?

The efficacy of ravulizumab (intravenous [IV] formulation; administered every 8 weeks) for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) has been demonstrated in randomized trials.

This ongoing pivotal phase 3 trial was designed to compare the pharmacokinetic (PK) non-inferiority of the ravulizumab on-body delivery system for subcutaneous (SUBQ) administration (self-administered weekly) with IV ravulizumab in patients with PNH who were clinically stable on prior IV eculizumab therapy.

What was learned from the study?

In patients with PNH, treatment with SUBQ ravulizumab achieved PK non-inferiority compared with IV ravulizumab for the primary endpoint of day 71 serum ravulizumab trough concentration (C_{trough}).

Through 1 year of SUBQ ravulizumab treatment, ravulizumab C_{trough} levels were maintained above the previously established PK threshold and free complement component 5 (C5) levels below the defined pharmacodynamic threshold; all efficacy endpoints remained stable over time, and patients reported increased satisfaction with SUBQ ravulizumab (compared with IV eculizumab).

Patients may be switched from IV eculizumab or IV ravulizumab to SUBQ ravulizumab without loss of efficacy, demonstrating that the SUBQ route of administration provides an additional treatment choice for patients with PNH receiving complement C5 inhibitor therapy.

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, chronic, and life-threatening hematologic disorder caused by uncontrolled activation of the terminal complement pathway, leading to intravascular hemolysis, a prothrombotic state, and increased morbidity and mortality [1–3]. In untreated patients, the clinical symptoms of PNH are associated with reduced health-related quality of life (HRQoL) and increased incidence of hospitalization, risk of thrombosis, and death [3, 4].

The development of targeted complement component 5 (C5) inhibitors has improved survival for patients with PNH to a level similar to that of the general population [5]. Eculizumab, a first-in-class complement C5 inhibitor (intravenous [IV] administration every 2 weeks), was the first disease-specific treatment to be approved for patients with PNH (first approved in 2007 for PNH, and is also approved for atypical hemolytic–uremic syndrome [aHUS]) [6, 7]. Ravulizumab (IV formulation, first approved in 2018 for PNH and 2019 for aHUS),

a long-acting C5 inhibitor [8], is currently approved as a treatment for adult and pediatric patients with PNH or aHUS [9–11]. The long duration of action of ravulizumab enables IV dosing every 8 weeks, resulting in a significantly lower number of infusions per year than eculizumab [8, 12, 13].

The subcutaneous (SUBQ) formulation ravulizumab with on-body delivery system (OBDS) was approved in the USA for adult patients with PNH or aHUS in 2022 for once weekly self-administration [9]. The ravulizumab OBDS for SUBQ administration consists of a pre-filled cartridge that adheres to the body and enables self-administration by pushing a button. A recent modeling analysis estimated that SUBQ ravulizumab may reduce time spent receiving therapy and costs associated with productivity losses compared with IV administration, with benefits to both patients and caregivers [14].

The relationship between pharmacokinetic (PK) exposure and clinical efficacy of IV ravulizumab in patients with PNH has been established in prior clinical studies [12, 13]. Study 303 (NCT03748823) is an ongoing pivotal phase 3 trial designed to evaluate the PK non-inferiority of SUBQ ravulizumab compared with IV ravulizumab in patients with PNH, who were clinically stable and had received IV eculizumab therapy for at least 3 months prior to study entry. The study was also designed to demonstrate the pharmacodynamics (PD), efficacy, safety, and immunogenicity of SUBQ ravulizumab over time, as well as the performance of the ravulizumab OBDS for SUBQ administration.

METHODS

Study Design

Study 303 is an ongoing phase 3, randomized, open-label, multicenter study to confirm the PK non-inferiority of SUBQ ravulizumab compared with IV ravulizumab in adult patients with PNH who received IV eculizumab treatment (900 mg every 2 weeks) for at least 3 months prior to study entry. The study was conducted at 51 centers across 14 countries and consisted of an

up to 30-day screening period, a 10-week randomized treatment period, and an initial extension period of 42 weeks that was extended up to 172 weeks (Fig. 1).

During the randomized treatment period, patients were stratified by weight groups (≥ 40 kg to < 60 kg and ≥ 60 kg to < 100 kg) and then randomly assigned in a 2:1 ratio to receive either SUBQ ravulizumab or IV ravulizumab. Patients assigned to the SUBQ ravulizumab group received a weight-based loading dose of IV ravulizumab on day 1, followed by once weekly maintenance doses of SUBQ ravulizumab starting on day 15 through to completion of the randomized treatment period (day 71). Patients assigned to the IV ravulizumab group received a weight-based loading dose of IV ravulizumab on day 1 and a maintenance dose of IV ravulizumab on day 15. The IV ravulizumab loading and maintenance doses were 2400 mg and 3000 mg, respectively, for patients weighing ≥ 40 kg to < 60 kg, and 2700 mg and 3300 mg, respectively, for patients weighing ≥ 60 kg to < 100 kg. The SUBQ ravulizumab maintenance dose was 490 mg (administered via two ravulizumab OBDS for SUBQ

administration kits) for all patients (≥ 40 kg to < 100 kg).

After completion of the randomized treatment period (day 71), all patients were offered to continue receiving weekly SUBQ ravulizumab maintenance doses during the extension period (Fig. 1). Therefore, patients randomized to receive IV ravulizumab during the randomized treatment period had their first dose of SUBQ ravulizumab at the start of the extension period (day 71) (referred to as the IV/SUBQ group); patients randomized to SUBQ ravulizumab received SUBQ treatment during the randomized treatment period (starting on day 15) and the extension period (referred to as the SUBQ/SUBQ group). Data from the 10-week randomized treatment period and the first year of SUBQ ravulizumab treatment (except for patients who withdrew prematurely) are presented in the current analysis.

The study was conducted in accordance with the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines. The protocol was approved by the institutional review board or independent ethics committee at each participating center (Supplementary Material

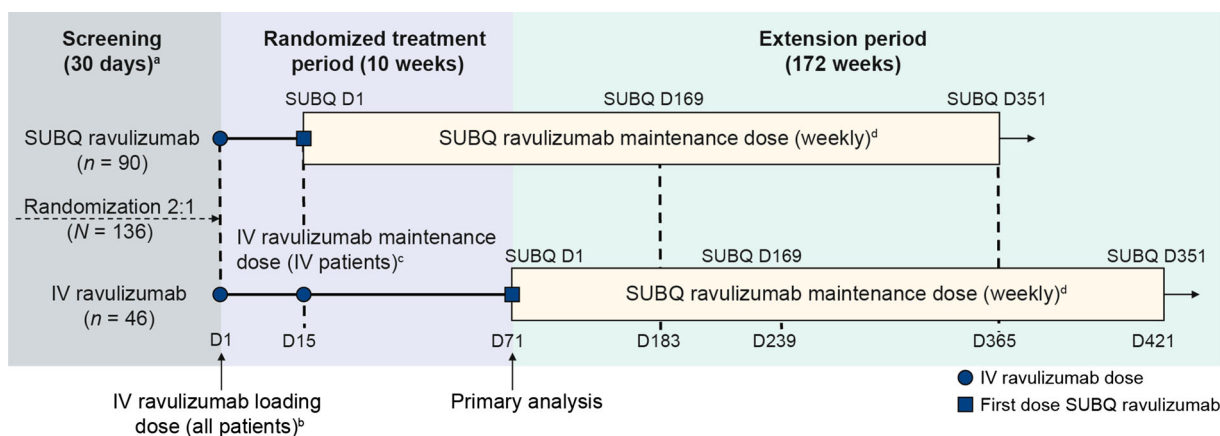


Fig. 1 Schematic of study design and treatment formulations received during the randomized treatment period and SUBQ treatment. ^aPatients on eculizumab ≥ 3 months. ^bThe ravulizumab IV loading dose was 2400 mg for patients weighing ≥ 40 kg to < 60 kg and 2700 mg for patients weighing ≥ 60 kg to < 100 kg. ^cThe ravulizumab IV maintenance dose was 3000 mg for patients weighing

≥ 40 kg to < 60 kg and 3300 mg for patients weighing ≥ 60 kg to < 100 kg. ^dThe ravulizumab SUBQ maintenance dose was 490 mg (administered via two ravulizumab OBDS for SUBQ administration devices) for all patients (≥ 40 kg to < 100 kg). *D* day, *IV* intravenous, *OBDS* on-body delivery system, *SUBQ* subcutaneous

Table S1), and all patients provided informed consent to participate in the study.

Patients

This study enrolled patients of at least 18 years of age with a body weight ≥ 40 kg but < 100 kg who had a documented diagnosis of PNH confirmed by high-sensitivity flow cytometry evaluation and had been vaccinated against meningococcal infection in the 3 years prior to, or at the time of, initiating the study drug. Patients must have received ongoing IV eculizumab treatment for at least 3 months prior to study entry (with no missed doses within 2 months and no more than two doses outside of the visit window) and have lactate dehydrogenase (LDH) levels no more than 1.5 times the upper limit of normal (ULN; 281 U/L for men and 330 U/L for women) at screening. Patients were excluded if they had more than one LDH value greater than two times the ULN in the 3 months prior to study entry, a major adverse vascular event (MAVE) in the 6 months prior to study entry, a platelet count less than $30,000/\text{mm}^3$, or a neutrophil count less than $500/\mu\text{L}$ at screening.

Outcomes

The primary endpoint was day 71 serum ravulizumab trough concentration (C_{trough}). Secondary PK/PD endpoints included SUBQ ravulizumab PK and PD, as measured by ravulizumab C_{trough} and serum free C5 concentrations over time through 1 year of SUBQ treatment, respectively.

Secondary efficacy endpoints included change in LDH from baseline, incidence of breakthrough hemolysis (BTH), achievement of transfusion avoidance, achievement of stabilized hemoglobin, change in clinical manifestations of PNH, reticulocyte count, estimated glomerular filtration rate (eGFR), and change in PNH red blood cell (RBC) clone size over time. Efficacy endpoints were measured over time through 1 year of SUBQ treatment; PNH RBC

clone size was only measured during the randomized treatment period. BTH was defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], MAVE [including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH of at least two times the ULN, as assessed by the central laboratory. Transfusion avoidance was defined as patients who remained transfusion-free and did not require a transfusion after the first dose of study drug. Stabilized hemoglobin was defined as avoidance of an at least 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion from baseline to the end of the period of interest.

HRQoL and treatment administration satisfaction were assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue subscale version 4.0 (range 0–52; higher scores indicate less fatigue) [15], the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) version 3.0 (range 0–100; higher scores represent a higher response level) [16], and the Treatment Administration Satisfaction Questionnaire (TASQ) (consists of 19 individual items to evaluate different aspects of treatment administration; lower scores indicate a more positive response) [17]. Baseline scores for the FACIT-Fatigue, EORTC QLQ-C30, and TASQ measures were representative of ongoing IV eculizumab treatment at study entry.

Safety, including adverse events (AEs), serious AEs (SAEs), and adverse device effects (ADEs), was assessed up to the 52-week data cutoff. ADEs were defined as AEs related to the investigational medical device, including any AEs resulting from a missed dose, partial dose, or other device-related issues. ADEs not related to drug delivery included local administration site reactions (infusion site/injection site reactions) and systemic reactions considered to be related to the investigational medical device. Device performance and device complaints were also assessed up to data cutoff.

Immunogenicity was measured through 1 year of SUBQ treatment.

Statistical Analysis

PK analyses were performed on the PK analysis set, which comprised all patients who had evaluable PK data for whom all doses up to day 64 were compliant with the planned dose and protocol-specified dosing time windows, and the predose PK sample on day 71 was collected in ± 3 h from the nominal time of the first dose on day 1. PD analyses were performed on all patients who received at least one dose of study drug and who had evaluable PD data. Efficacy analyses were performed on the full analysis set (all randomized patients who received at least one dose of ravulizumab). Safety analyses were performed on the safety analysis set (all patients who received at least one dose of ravulizumab). For the SUBQ treatment period, only SUBQ treated patient populations were used, and all endpoints were based on the start of SUBQ treatment for each patient (day 15 for SUBQ/SUBQ group; day 71 for IV/SUBQ group).

The planned sample size of 105 evaluable patients (70 in the SUBQ ravulizumab group and 35 in the IV ravulizumab group) would provide 90% power to detect non-inferiority using a one-sided test at an alpha level of 0.05 and a PK non-inferiority margin of 0.8. Patients continued to be enrolled while the prespecified sample size re-estimation interim analysis was in progress, and actual enrollment ($N = 136$) exceeded the targeted enrollment ($N = 105$, with a maximum of 144 patients). A weighted Cui–Hung–Wang test statistic based on an analysis of variance, with treatment and categorical weight group as fixed effects, was used to calculate the 90% confidence interval (CI) of the geometric mean ratio, to avoid inflation of type I error due to the sample size re-estimation interim analysis (no adjustments were made to the sample size during the interim analysis). All analyses were performed using SAS (SAS Institute Inc, Cary, NC, USA) version 9.4 or higher, or other validated statistical software.

RESULTS

Patient Disposition, Demographics, and Baseline Clinical Characteristics

Of the 141 screened patients, 136 were randomized and treated with SUBQ ravulizumab ($n = 90$) or IV ravulizumab ($n = 46$, Supplementary Material Fig. S1). One patient in the IV group withdrew as a result of patient decision prior to completing the randomized treatment period, and one patient in the SUBQ group withdrew consent prior to entering the extension period. Of the 134 patients who entered the extension period, four completed the initial 42-week extension period and opted not to continue when the duration of the study was extended to 172 weeks, and five withdrew from the study (three withdrawn consent, one protocol deviation, and one death due to COVID-19). One patient in the SUBQ group discontinued study treatment after undergoing allogeneic stem cell transplantation but observation continued until the data cutoff date. Seven patients (SUBQ group, $n = 6$; IV group, $n = 1$) from a non-compliant investigative site were excluded from all prespecified analyses because of important source documentation deviations.

Patient demographics and baseline characteristics were balanced between treatment groups (Table 1). Median age at informed consent was 44.0 years (range 18–79 years); 53.5% of patients were female and 71.3% were White. The median time from PNH diagnosis to informed consent was 7.5 years (range 0.6–33.0 years). Fewer than 20% of patients had a transfusion in the year prior to first dose of study treatment, and one-third had a history of MAVE; median hemoglobin levels were 112.5 g/L (range 67.0–161.0 g/L) at screening and 112.0 g/L (range 58.0–160.0 g/L) at baseline.

Primary Endpoint

The geometric least-squares mean ratio of C_{trough} of SUBQ ravulizumab to IV ravulizumab at day 71 was 1.257 (90% CI 1.160–1.361; $p < 0.0001$). Treatment with SUBQ ravulizumab achieved PK non-inferiority compared with IV

Table 1 Patient demographics and baseline clinical characteristics (full analysis set)^a

| Variable | SUBQ ravulizumab (<i>n</i> = 84) | IV ravulizumab (<i>n</i> = 45) | Total (<i>N</i> = 129) |
|-----------------------------------------------------------------------------------------|--------------------------------------|------------------------------------|----------------------------|
| Median age, years (min, max) | 42.5 (18, 79) | 44.0 (24, 77) | 44.0 (18, 79) |
| Sex, <i>n</i> (%) | | | |
| Male | 40 (47.6) | 20 (44.4) | 60 (46.5) |
| Female | 44 (52.4) | 25 (55.6) | 69 (53.5) |
| Race, <i>n</i> (%) | | | |
| White | 63 (75.0) | 29 (64.4) | 92 (71.3) |
| Black or African American | 3 (3.6) | 4 (8.9) | 7 (5.4) |
| Asian | 0 | 2 (4.4) | 2 (1.6) |
| American Indian or Alaska Native | 0 | 1 (2.2) | 1 (0.8) |
| Other | 4 (4.8) | 2 (4.4) | 6 (4.7) |
| Not reported | 13 (15.5) | 6 (13.3) | 19 (14.7) |
| Unknown | 1 (1.2) | 1 (2.2) | 2 (1.6) |
| Baseline weight, <i>n</i> (%) | | | |
| ≥ 40 to < 60 kg | 13 (15.5) | 8 (17.8) | 21 (16.3) |
| ≥ 60 to < 100 kg | 71 (84.5) | 37 (82.2) | 108 (83.7) |
| Median time from diagnosis to informed consent, years (min, max) | 7.5 (0.8, 33.0) | 7.9 (0.6, 29.0) | 7.5 (0.6, 33.0) |
| PNH clone size %, mean (SD) | | | |
| Total RBCs | 44.8 (34.6) | 55.0 (33.4) | 48.4 (34.3) |
| Granulocyte | 74.0 (27.5) | 83.2 (20.6) | 77.2 (25.6) |
| Monocytes | 77.2 (26.6) | 85.7 (18.6) | 80.2 (24.3) |
| Number of patients with transfusions within 1 year prior to first dose, <i>n</i> (%) | 13 (15.5) | 11 (24.4) | 24 (18.6) |
| Patients with prior PNH-associated conditions, <i>n</i> (%) | 78 (92.9) | 41 (91.1) | 119 (92.2) |
| Patients with a history of MAVE, <i>n</i> (%) | 26 (31.0) | 17 (37.8) | 43 (33.3) |

^aPatients included in the study were clinically stable on IV eculizumab for at least 3 months prior to study entry
IV intravenous, *MAVE* major adverse vascular events, *PD* pharmacodynamic, *PK* pharmacokinetic, *PNH* paroxysmal nocturnal hemoglobinuria, *RBC* red blood cell, *SD* standard deviation, *SUBQ* subcutaneous

ravulizumab for the primary endpoint, with the 90% CI lower limit (1.160) exceeding the pre-specified non-inferiority boundary (0.8). Mean (standard deviation [SD]) day 71 C_{trough} estimate after identical weight-based IV

ravulizumab dosing was 457.6 (108.5) $\mu\text{g/mL}$, establishing assay sensitivity in support of the findings of non-inferiority (mean [SD] day 71 C_{trough} in the pivotal phase 3 study, conducted in an eculizumab-experienced PNH patient

population, was 481.1 [127.3] $\mu\text{g/mL}$ [18, 19]. The PK non-inferiority of SUBQ ravulizumab compared with IV ravulizumab was consistent across all prespecified sensitivity analyses (Supplementary Material Fig. S2).

Secondary PK/PD Endpoints

In both the SUBQ ravulizumab and IV ravulizumab treatment groups, all individual serum ravulizumab concentrations were greater than 175 $\mu\text{g/mL}$ (the previously established PK threshold for achieving and sustaining complete terminal complement inhibition) (Fig. 2) and all individual serum free C5 concentrations were less than 0.5 $\mu\text{g/mL}$ (the defined threshold for complete terminal complement inhibition) (Supplementary Material Fig. S3) during the randomized treatment period (through day 71) [20]. After initiation of SUBQ treatment (day 15 for the SUBQ/SUBQ group and day 71 for the IV/SUBQ group), ravulizumab C_{trough} levels more than 175 $\mu\text{g/mL}$ and free C5 levels less than 0.5 $\mu\text{g/mL}$ were observed in all patients at all sampling times through 1 year of SUBQ administration.

Secondary Efficacy Endpoints

During the randomized treatment period (through day 71), efficacy endpoints remained stable in both the SUBQ ravulizumab and IV ravulizumab groups (Table 2). Mean (SD) percentage change in LDH from baseline to day 71 was 2.6% (33.9%) for the SUBQ group and 5.7% (29.7%) for the IV group. LDH levels remained stable over time in both treatment groups (Fig. 3). There was a single BTH event in each group during this 71-day period. Neither of the BTH events was associated with suboptimal C5 inhibition (defined as free C5 \geq 0.5 $\mu\text{g/mL}$). The patient in the SUBQ group had a grade 1 viral infection that preceded the BTH event. A similar proportion of patients in each treatment group achieved transfusion avoidance (SUBQ group, 94.0%; IV group, 86.7%;) and stabilized hemoglobin (SUBQ group, 93.6%; IV group, 81.8%). The percentage of patients with any clinical manifestations of PNH was similar in both treatment groups (SUBQ group, 47.6%; IV

group, 46.7%); fatigue was the most common symptom (SUBQ group, 34/40 [85.0%]; IV group, 18/21 [85.7%]). Reticulocyte count, eGFR, and total PNH RBC clone size remained stable over time in both treatment groups.

Efficacy endpoints remained stable over time through 1 year of SUBQ ravulizumab treatment in both the SUBQ/SUBQ and IV/SUBQ groups. LDH levels were stable and the mean percentage change in LDH from baseline to SUBQ day 351 was 0.9% (SUBQ/SUBQ group, 1.7%; IV/SUBQ group, -0.8%). It should be noted that wide confidence intervals for some time points during SUBQ ravulizumab treatment are likely owing to outlier data points (Fig. 3). One male patient with LDH > 1.5 times ULN on SUBQ day 295 had a BTH event that day; median LDH for all male patients at day 295 was 258 U/L (ULN for males = 281 U/L). One female patient with LDH > 1.5 times ULN on SUBQ day 337 had high LDH values throughout; median LDH for all female patients at SUBQ day 337 was 224 U/L (ULN for females = 330 U/L). BTH events were infrequent: 5/128 (3.9%) (SUBQ/SUBQ group, three events; IV/SUBQ group, two events). Infection was potentially associated with the BTH event in four patients; the fifth patient had a BTH event of unknown cause that remained unresolved at data cutoff. None of the events was associated with suboptimal C5 inhibition (free C5 \geq 0.5 $\mu\text{g/mL}$). Transfusion avoidance was maintained in 83.6% of patients (SUBQ/SUBQ group, 85.7%; IV/SUBQ group, 79.5%), and the majority (79.7%) achieved stabilized hemoglobin (SUBQ/SUBQ group, 83.5%; IV/SUBQ group, 72.7%). Clinical manifestations of PNH were experienced by 58.6% of patients (SUBQ/SUBQ group, 63.1%; IV/SUBQ group, 50.0%); fatigue was the most common symptom (SUBQ/SUBQ group, 27/28 [96.4%]; IV/SUBQ group, not applicable). Reticulocyte count and eGFR remained stable over time in both treatment groups.

HRQoL and Treatment Administration Satisfaction Outcomes

The mean (SD) FACIT-Fatigue subscale scores at baseline were similar between treatment groups

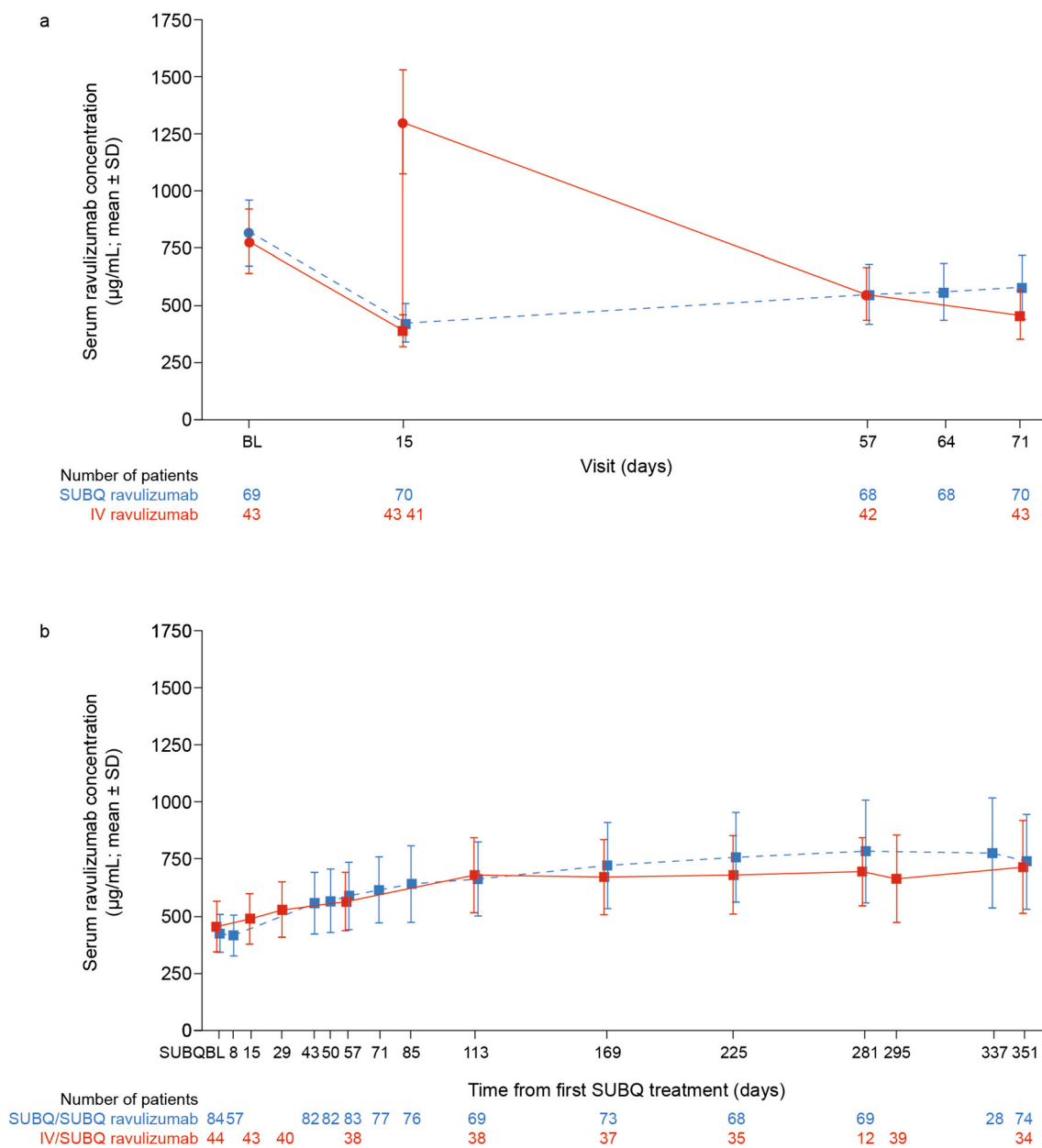


Fig. 2 Serum ravulizumab concentration (mean [SD]) over time during **a** the randomized treatment period (PK analysis set) and **b** the SUBQ treatment period (SUBQ treated full analysis set). BL was defined as the last assessment from the central laboratory prior to first dose of study drug. Circle = postdose sample; square = predose sample. The SUBQ group had samples collected predose at days 1, 15, 57, 64, and 71, and postdose at day 1. The IV

group had samples collected predose at days 1, 15 and 71, postdose at days 1 and 15, and any time at day 57. SUBQBL was defined as the last assessment from the central laboratory prior to first dose of SUBQ treatment. BL baseline, IV intravenous, PK pharmacokinetics, SD standard deviation, SUBQ subcutaneous, SUBQBL subcutaneous baseline

Table 2 Summary of efficacy endpoints through the randomized treatment period (full analysis set) and SUBQ treatment period (SUBQ treated full analysis set)

| | Randomized treatment period (through day 71) | | SUBQ treatment period (through SUBQ day 351) ^a | | |
|------------------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-----------------------------------------------------------|---------------------------------------------------|-------------------------------------------------|
| | SUBQ ravulizumab (<i>n</i> = 84) | IV ravulizumab (<i>n</i> = 45) | SUBQ/SUBQ ravulizumab ^b (<i>n</i> = 84) | IV/SUBQ ravulizumab ^b (<i>n</i> = 44) | Total (<i>N</i> = 128) |
| Percentage change in LDH from baseline, mean (SD) [95% CI] | (<i>n</i> = 82) 2.6 (33.9) [− 4.9, 10.0] | (<i>n</i> = 43) 5.7 (29.7) [− 3.4, 14.9] | (<i>n</i> = 73) 1.7 (21.9) [− 3.4, 6.9] | (<i>n</i> = 34) − 0.8 (17.2) [− 6.8, 5.2] | (<i>N</i> = 107) 0.9 (20.5) [− 3.0, 4.9] |
| BTH, <i>n</i> (%) [95% CI] | 1 (1.2) [0.0, 6.5] | 1 (2.2) [0.1, 11.8] | 3 (3.6) [0.7, 10.1] | 2 (4.5) ^c [0.6, 15.5] | 5 (3.9) [1.3, 8.9] |
| Transfusion avoidance, <i>n</i> (%) [95% CI] | 79 (94.0) [86.7, 98.0] | 39 (86.7) [73.2, 95.0] | 72 (85.7) [76.4, 92.4] | 35 (79.5) [64.7, 90.2] | 107 (83.6) [76.0, 89.6] |
| Hemoglobin stabilization, <i>n</i> (%) [95% CI] | (<i>n</i> = 78) 73 (93.6) [85.7, 97.9] | (<i>n</i> = 44) 36 (81.8) [67.3, 91.8] | (<i>n</i> = 79) 66 (83.5) [73.5, 90.9] | (<i>n</i> = 44) 32 (72.7) [57.2, 85.0] | (<i>N</i> = 123) 98 (79.7) [71.5, 86.4] |
| Clinical manifestations of PNH, <i>n</i> (%) [95% CI] ^d | 40 (47.6) [36.6, 58.8] | 21 (46.7) [31.7, 62.1] | 53 (63.1) [51.9, 73.4] | 22 (50.0) [34.6, 65.4] | 75 (58.6) [49.6, 67.2] |
| Percentage change reticulocyte count from baseline, mean (SD) [95% CI] | (<i>n</i> = 64) 5.2 (22.7) [− 0.4, 10.9] | (<i>n</i> = 39) 3.1 (18.8) [− 3.0, 9.2] | (<i>n</i> = 55) 6.1 (26.3) [− 1.0, 13.2] | (<i>n</i> = 29) 0.4 (19.5) [− 7.0, 7.8] | (<i>N</i> = 84) 4.1 (24.2) [− 1.1, 9.4] |
| Percentage change eGFR from baseline, mean (SD) [95% CI] | (<i>n</i> = 82) 3.7 (16.2) [0.1, 7.2] | (<i>n</i> = 43) 9.2 (20.0) [3.1, 15.4] | (<i>n</i> = 73) 8.0 (21.0) [3.1, 12.9] | (<i>n</i> = 34) − 2.1 (12.6) [− 6.6, 2.3] | (<i>N</i> = 107) 4.8 (19.3) [1.1, 8.5] |

Table 2 continued

| | Randomized treatment period (through day 71) | | SUBQ treatment period (through SUBQ day 351) ^a | | |
|----------------------------------------------|-------------------------------------------------|------------------------------------------------|-----------------------------------------------------------|---------------------------------------------------|-------------------------|
| | SUBQ ravulizumab (<i>n</i> = 84) | IV ravulizumab (<i>n</i> = 45) | SUBQ/SUBQ ravulizumab ^b (<i>n</i> = 84) | IV/SUBQ ravulizumab ^b (<i>n</i> = 44) | Total (<i>N</i> = 128) |
| Total PNH RBC clone size, mean (SD) [95% CI] | (<i>n</i> = 59) 43.4 (34.5) [0.7, 100.0] | (<i>n</i> = 34) 55.9 (32.3) [4.2, 98.0] | NA | NA | NA |

BTH breakthrough hemolysis, *CI* confidence interval, *eGFR* estimated glomerular filtration rate, *IV* intravenous, *LDH* lactate dehydrogenase, *NA* not applicable, *PNH* paroxysmal nocturnal hemoglobinuria, *SD* standard deviation, *SUBQ* subcutaneous

^aEndpoints for the SUBQ treatment period analyses were based on the start of SUBQ treatment for each patient

^bAll patients in both treatment groups received SUBQ ravulizumab during the SUBQ treatment period. Patients randomized to the SUBQ group during the randomized treatment period received their first dose of SUBQ ravulizumab on day 15. Patients randomized to receive IV ravulizumab during the randomized treatment period had their first dose of SUBQ ravulizumab at the start of the extension period (day 71)

^cIncludes one patient for whom response to “Breakthrough hemolysis experienced?” was entered as “Yes” using only a local laboratory LDH value

^dInvestigator or designee assessed each patient for signs and symptoms of PNH, which may include the following: fatigue, chest pain, abdominal pain, dyspnea, dysphagia, erectile dysfunction, and red/dark urine or hemoglobinuria

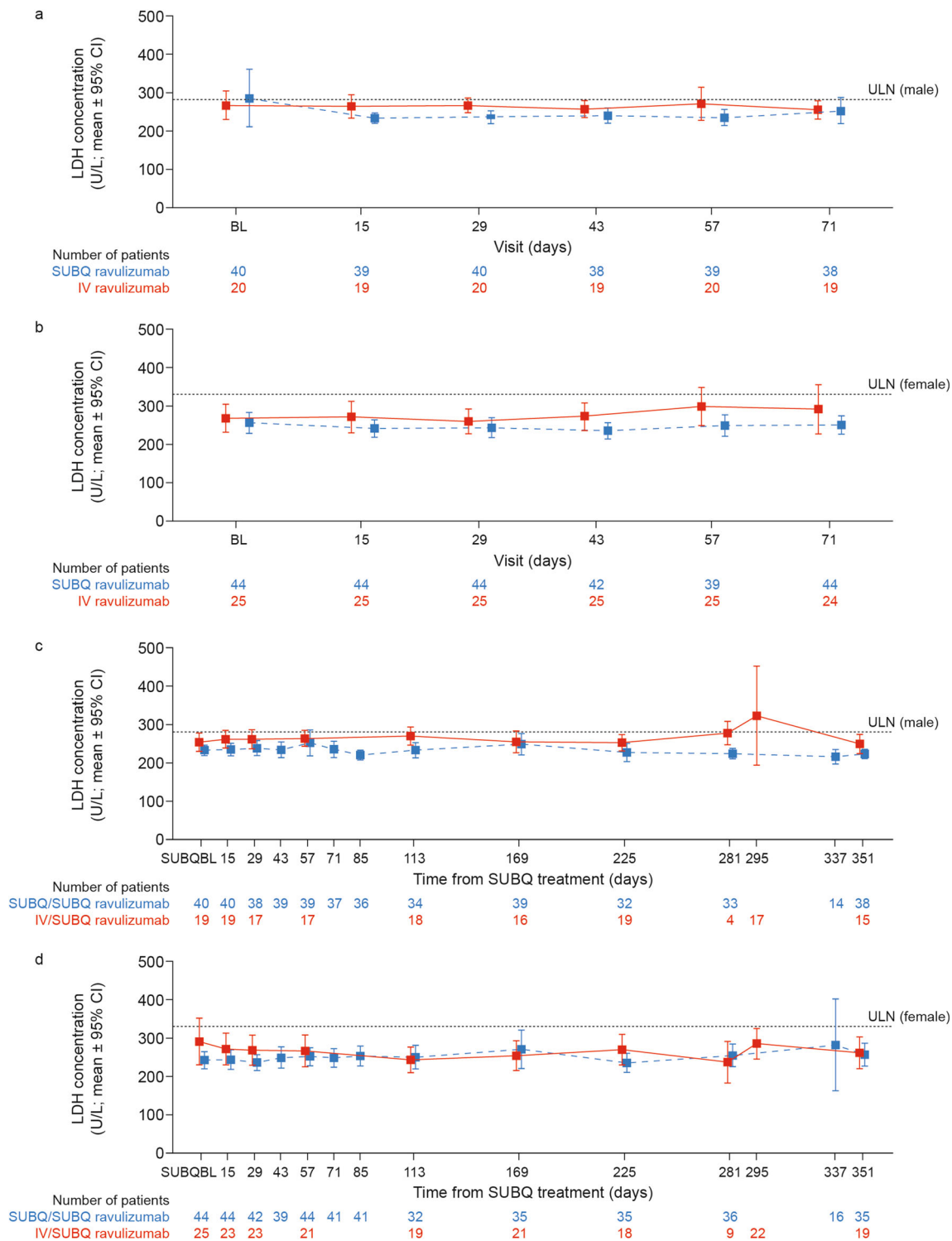
(SUBQ group, 40.3 [10.8]; IV group, 42.1 [10.3]) and remained stable through day 71 (Fig. 4). Mean EORTC QLQ-C30 global health status scores at baseline were also similar between treatment groups (SUBQ group, 74.1 [18.8]; IV group, 73.2 [19.4]) and remained stable through day 71 (Fig. 5). Mean FACIT-Fatigue and EORTC global health status scores were maintained through 1 year of SUBQ treatment.

The mean (SD) change in TASQ total score at day 71 compared with baseline was – 70.5 (70.5) for the SUBQ group compared with – 7.0 (34.6) for the IV group, indicating an increased treatment administration satisfaction with SUBQ (lower score indicates positive response). Mean (SD) total TASQ scores at baseline, based on the IV route of administration for eculizumab, were similar between treatment groups (SUBQ group, 152.2 [72.5]; IV group, 135.1 [63.8]). During the SUBQ treatment period, improvement in total TASQ score was apparent at the first post-treatment assessment with

SUBQ treatment (SUBQ day 29), with mean (SD) change in total score of – 63.2 (78.4) (Fig. 6). In the SUBQ/SUBQ group, increased satisfaction with the SUBQ route of administration compared with IV eculizumab administration was maintained through 1 year of SUBQ treatment. The mean (SD) change in total TASQ score at SUBQ day 351 compared with SUBQ baseline was – 69.3 (80.1) in the SUBQ/SUBQ group (IV/SUBQ group, data not available).

Safety

AEs during the randomized treatment period were similar in the SUBQ ravulizumab and IV ravulizumab groups when ADEs were excluded (SUBQ group, 64.3%; IV group, 60.0%) (Table 3). The most frequently reported AE (reported by at least 10% of patients, apart from the ADEs related to device product issues) among all patients was headache, which



◀**Fig. 3** LDH (U/L) mean (95% CI) values during the randomized treatment period by **a** male and **b** female (full analysis set) and during the SUBQ treatment period by **c** male and **d** female (SUBQ treated full analysis set). BL was defined as the last assessment from the central laboratory prior to first dose of study drug. SUBQBL was defined as the last assessment from the central laboratory prior to first dose of SUBQ treatment (SUBQ/SUBQ group = day 15 and IV/SUBQ group = day 71 predose). Dotted horizontal lines indicate the ULN; ULN for male = 281 U/L; ULN for female = 330 U/L. Outliers were responsible for wide confidence intervals at some timepoints. One male patient with LDH > 1.5 times ULN on SUBQ day 295 had a BTH event that day; median LDH for all male patients at day 295 was 258 U/L. One female patient with LDH > 1.5 times ULN on SUBQ day 337 had high LDH values throughout; median LDH for all female patients at SUBQ day 337 was 224 U/L. *BL* baseline, *CI* confidence interval, *IV* intravenous, *LDH* lactate dehydrogenase, *SUBQ* subcutaneous, *SUBQBL* subcutaneous baseline, *ULN* upper limit of normal

occurred in 13.1% of patients in the SUBQ group and 8.9% of patients in the IV group. Other AEs occurring in at least 5% of patients overall were diarrhea, abdominal pain, nausea, and nasopharyngitis. Most AEs were grade 1 or grade 2 in severity. Five patients experienced grade 3 AEs (SUBQ group: anemia and hemolysis in one patient, and lens dislocation and cervicobrachial syndrome in one patient each; IV group: dental caries in one patient, and cholecystitis and cholelithiasis in one patient). One patient in the SUBQ group experienced a grade 4 SAE of neutropenia (recovered, not related to study treatment). During the SUBQ treatment period, the most common AEs (reported by at least 10% of patients, apart from the ADEs related to device product issues) were headache (14.1%), COVID-19 (14.1%), and pyrexia (10.9%). All events of headache were grade 1 or 2. One patient in the SUBQ/SUBQ group died during the SUBQ treatment period as a result of COVID-19. At least one treatment-emergent SAE was experienced by 21.1% of patients during SUBQ treatment.

Immunogenicity

No treatment-emergent anti-drug antibodies were observed during 1 year of SUBQ ravulizumab administration.

ADEs During SUBQ Treatment

During the randomized treatment period (through day 71), 46.4% of patients in the SUBQ ravulizumab group experienced an ADE (Table 3); no serious ADEs were reported. The most frequently reported ADEs included injection site reaction (6.0%), injection site erythema (4.8%), and medical device site erythema (3.6%; includes redness where tape of the device attaches to the skin, left thigh erythema, both thigh erythema, and sensitivity to device adhesive [mild erythema]). The remainder of the ADEs (33/110 events) during this period were related to issues with the device product (no dose/less than full dose).

As of the 52-week data cutoff, 74.2% of patients treated with SUBQ ravulizumab experienced an ADE. Of patients who experienced an ADE, most events (238/373 events) were related to a device product issue. ADEs not related to a device product issue were reported by 22.7% of patients during SUBQ treatment. The most frequently reported ADEs unrelated to a device product issue were injection site reaction (4.7%), medical device site erythema (3.9%), infusion site erythema (3.1%), and injection site erythema (3.1%).

The incidence of local administration site reactions and ADEs related to drug delivery decreased over time (0–6 months, 197.4 and 192.6 events per 100 patient-years; > 6 to 12 months, 13.2 and 152.0 events per 100 patient-years). One patient had two serious ADEs of application site induration and procedural hypotension during the SUBQ treatment period. Although many patients had at least one ADE relating to drug delivery, full dose administration was achieved in 99.9% (8459/8464 administration attempts) of SUBQ ravulizumab administration attempts.

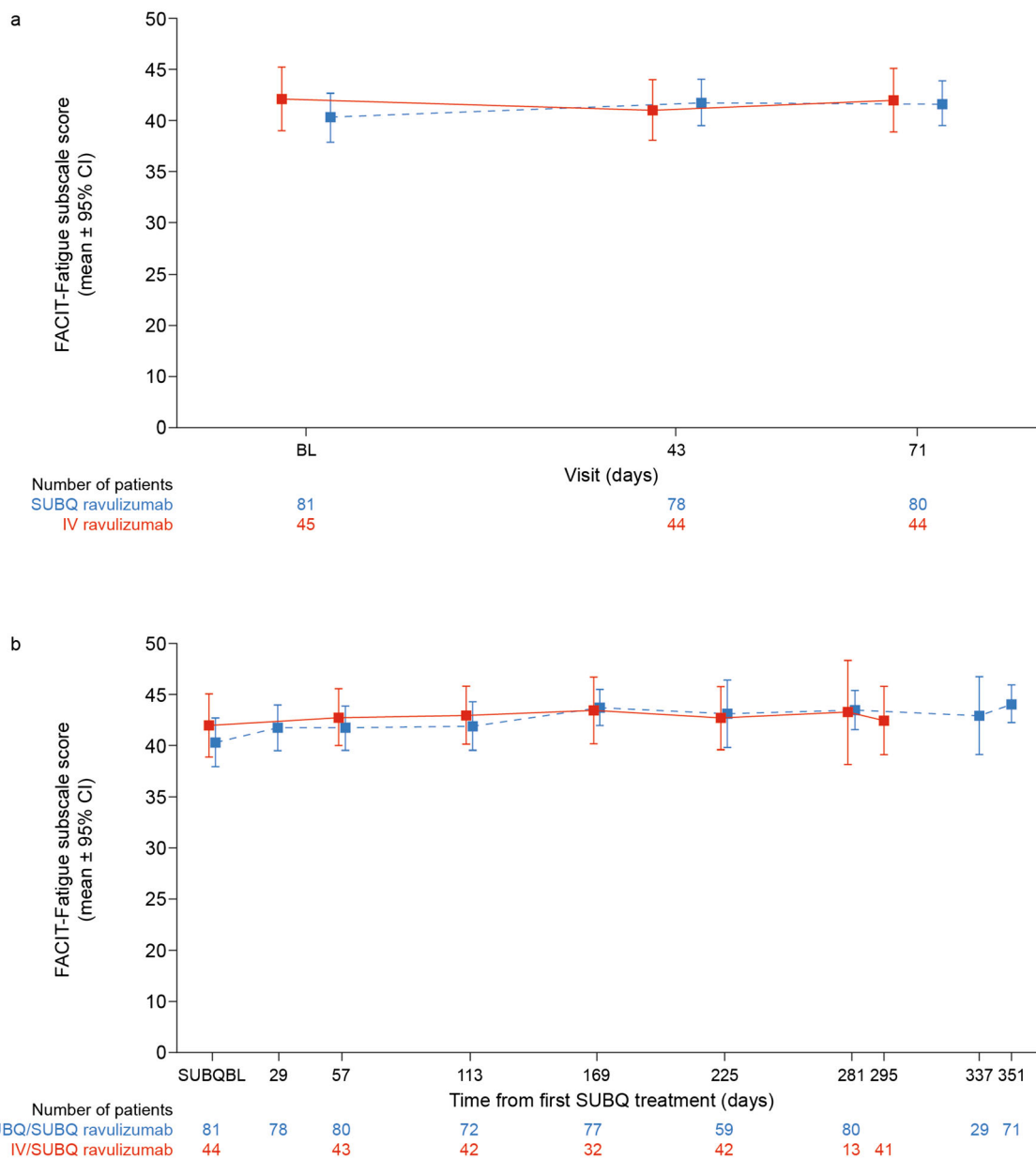


Fig. 4 FACIT-Fatigue subscale score mean (95% CI) values during **a** the randomized treatment period (full analysis set) and **b** the SUBQ treatment period by treatment group (SUBQ treated full analysis set). BL was defined as the last assessment prior to first dose of study drug. Patients enrolled in the study were clinically stable on IV eculizumab prior to study entry. SUBQBL was defined as the last assessment prior to first dose of

SUBQ treatment. FACIT subscale score ranges from 0 to 52, with a higher score indicating less fatigue. The mean FACIT-Fatigue score for the general population is 43.5 [21, 22]. BL baseline, CI confidence interval, FACIT-Fatigue Functional Assessment of Chronic Illness Therapy-Fatigue, IV intravenous, SUBQ subcutaneous, SUBQBL subcutaneous baseline

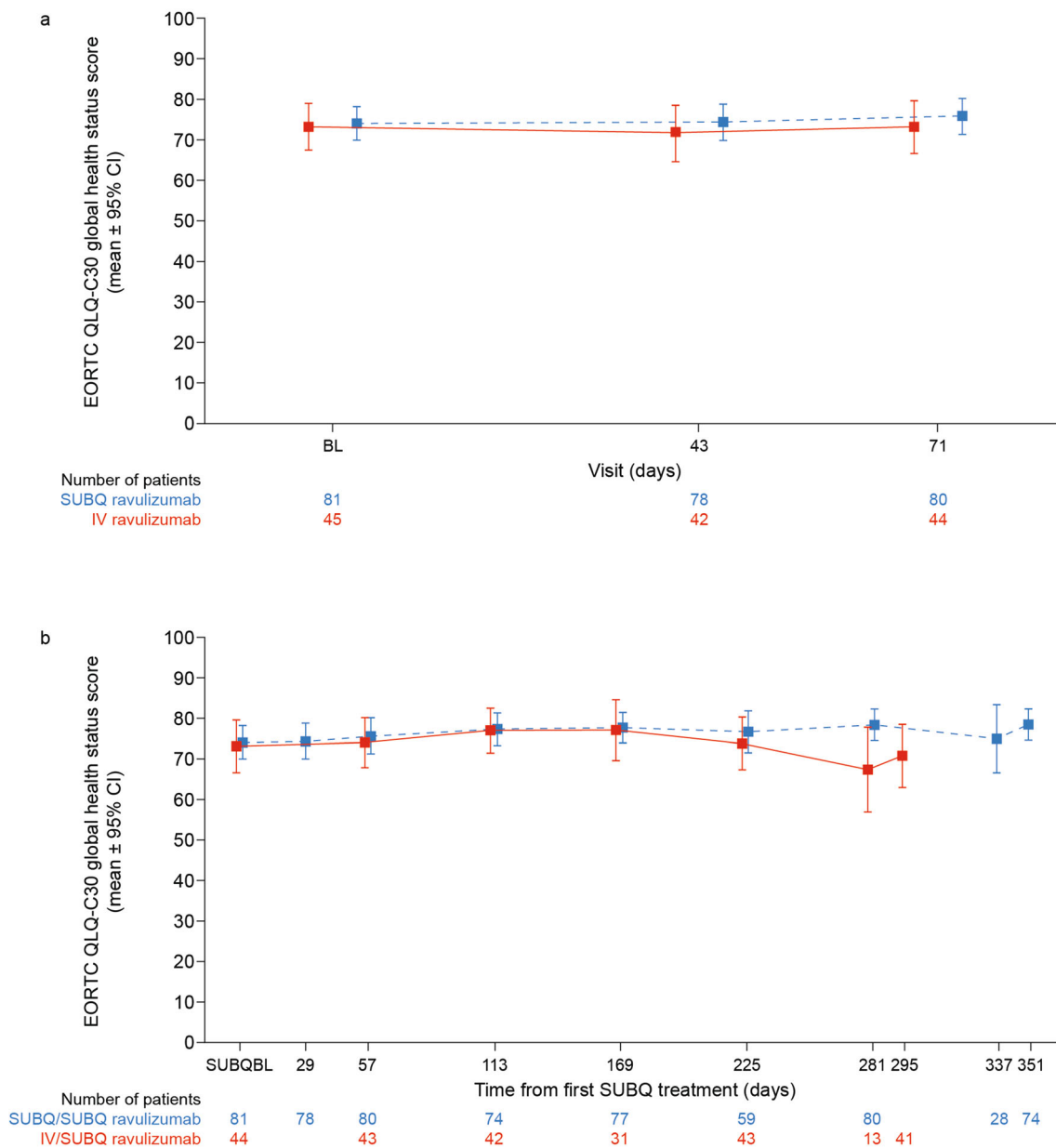


Fig. 5 EORTC QLQ-C30 global health status score mean (95% CI) values during **a** the randomized treatment period (full analysis set) and **b** the SUBQ treatment period by treatment group (SUBQ treated full analysis set). BL was defined as the last assessment prior to first dose of study drug. Patients enrolled in the study were clinically stable on IV eculizumab prior to study entry. SUBQBL was defined as the last assessment prior to first dose of

SUBQ treatment. Each subscale has a range of 0–100%, with a high score representing a higher response level. The mean EORTC QLQ-C30 global health status score for the general population is 75.9 [23]. BL baseline, CI confidence interval, EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30, IV intravenous, SUBQ subcutaneous, SUBQBL subcutaneous baseline

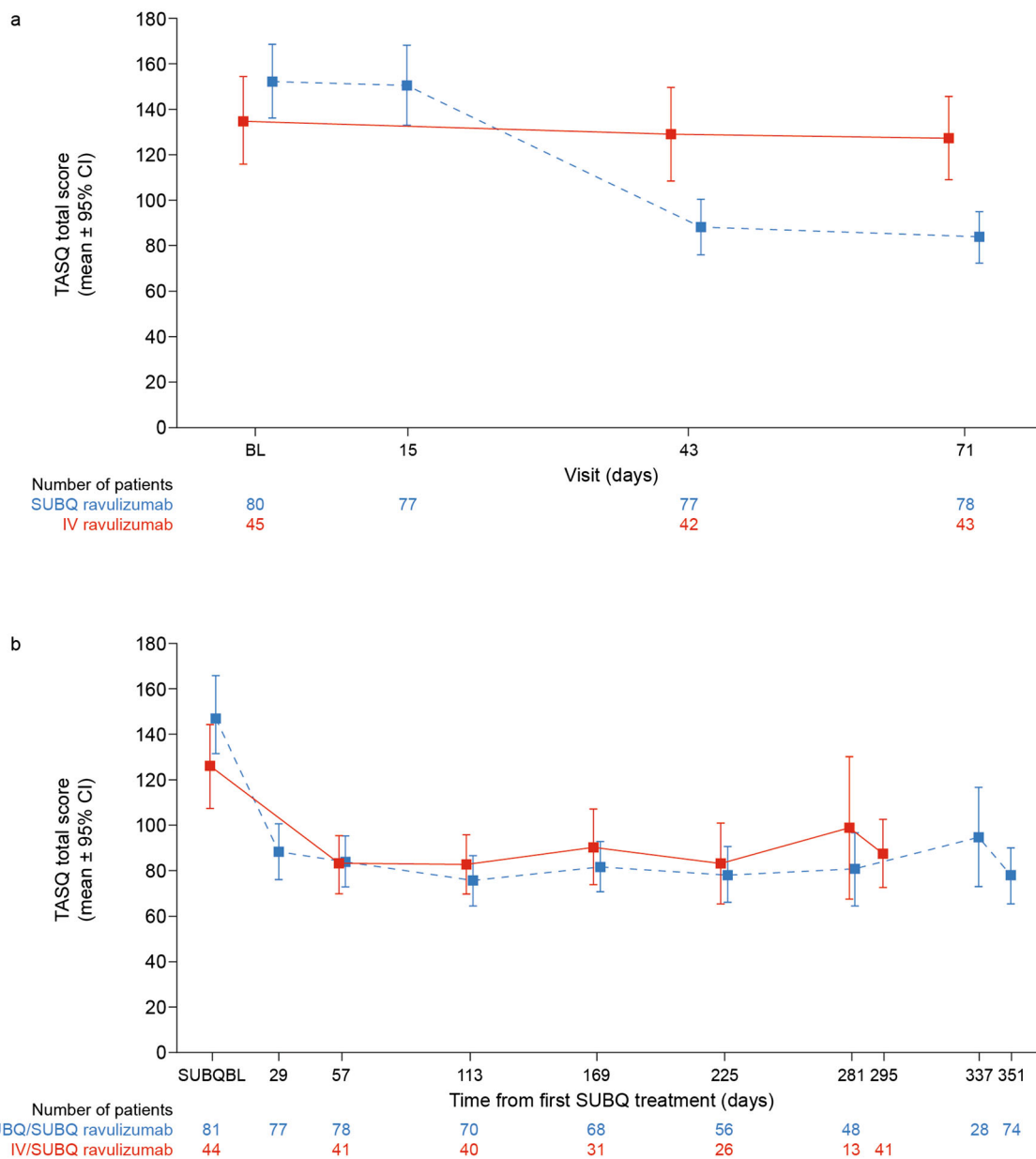


Fig. 6 Mean (95% CI) total TASQ score during **a** the randomized treatment period (full analysis set) and **b** the SUBQ treatment period (SUBQ-treated full analysis set). BL was defined as the last non-missing value prior to the first dose of study drug. At BL and on day 15, the TASQ-IV was completed for the SUBQ group. SUBQBL was defined as the last assessment prior to first dose of SUBQ treatment. Patients enrolled in the study were clinically

stable on IV eculizumab prior to study entry. The TASQ-IV questionnaire was completed at SUBQBL, which is study day 15 for the SUBQ ravulizumab group and study day 71 for the IV ravulizumab group. *BL* baseline, *CI* confidence interval, *IV* intravenous, *SD* standard deviation, *SUBQ* subcutaneous, *SUBQBL* subcutaneous baseline, *TASQ* Treatment Administration Satisfaction Questionnaire

Table 3 Summary of safety during the randomized treatment period (safety analysis set) and SUBQ treatment period (SUBQ treated safety analysis set)

| Patients with AEs, <i>n</i> (%) | Randomized treatment period (through day 71) | | | SUBQ treatment period (through SUBQ day 351) | | |
|----------------------------------------------------------|-------------------------------------------------|---------------------------------------|----------------------------|-------------------------------------------------|--------------------------------------------|----------------------------|
| | SUBQ ravulizumab (<i>n</i> = 84) | IV ravulizumab (<i>n</i> = 45) | Total (<i>N</i> = 129) | SUBQ/SUBQ ravulizumab (<i>n</i> = 84) | IV/SUBQ ravulizumab (<i>n</i> = 44) | Total (<i>N</i> = 128) |
| Any AE | 67 (79.8) | 27 (60.0) | 94 (72.9) | 82 (97.6) | 42 (95.5) | 124 (96.9) |
| Any SAE | 5 (6.0) | 1 (2.2) | 6 (4.7) | 17 (20.2) | 10 (22.7) | 27 (21.1) |
| Death | 0 | 0 | 0 | 1 (1.2) | 0 | 1 (0.8) |
| AEs leading to discontinuation of study drug | 0 | 0 | 0 | 0 | 1 (2.3) | 1 (0.8) |
| Any ADE ^a | 39 (46.4) | NA | 39 (30.2) | 60 (71.4) | 35 (79.5) | 95 (74.2) |
| Any serious ADE ^a | 0 | NA | 0 | 1 (1.2) | 0 | 1 (0.8) |
| ADEs that were not device issues ^a | 22 (26.2) | NA | 22 (17.1) | 22 (26.2) | 7 (15.9) | 29 (22.7) |
| ADEs that were device issues ^a | 21 (25.0) | NA | 21 (16.3) | 56 (66.7) | 35 (79.5) | 91 (71.1) |
| AEs not associated with device/device use | 54 (64.3) | 27 (60.0) | 81 (62.8) | 75 (89.3) | 38 (86.4) | 113 (88.3) |
| AEs by severity ^b | | | | | | |
| Grade 1 | 64 (76.2) | 21 (46.7) | 85 (65.9) | 78 (92.9) | 39 (88.6) | 117 (91.4) |
| Grade 2 | 20 (23.8) | 14 (31.1) | 34 (26.4) | 43 (51.2) | 23 (52.3) | 66 (51.6) |
| Grade 3 | 3 (3.6) | 2 (4.4) | 5 (3.9) | 12 (14.3) | 8 (18.2) | 20 (15.6) |
| Grade 4 | 1 (1.2) | 0 | 1 (0.8) | 5 (6.0) | 3 (6.8) | 8 (6.3) |
| Grade 5 | 0 | 0 | 0 | 1 (1.2) | 0 | 1 (0.8) |
| Most common AEs (in $\geq 5\%$ of patients) ^c | | | | | | |
| Headache | 11 (13.1) | 4 (8.9) | 15 (11.6) | 12 (14.3) | 6 (13.6) | 18 (14.1) |
| Diarrhea | 11 (13.1) | 2 (4.4) | 13 (10.1) | 11 (13.1) | 1 (2.3) | 12 (9.4) |
| Abdominal pain | 5 (6.0) | 3 (6.7) | 8 (6.2) | 7 (8.3) | 2 (4.5) | 9 (7.0) |
| Nausea | 5 (6.0) | 3 (6.7) | 8 (6.2) | 5 (6.0) | 1 (2.3) | 6 (4.7) |
| Nasopharyngitis | 5 (6.0) | 2 (4.4) | 7 (5.4) | 8 (9.5) | 4 (9.1) | 12 (9.4) |
| Pyrexia | 5 (6.0) | 0 | 5 (3.9) | 10 (11.9) | 4 (9.1) | 14 (10.9) |
| Back pain | 4 (4.8) | 2 (4.4) | 6 (4.7) | 7 (8.3) | 1 (2.3) | 8 (6.3) |

Table 3 continued

| Patients with AEs, <i>n</i> (%) | Randomized treatment period (through day 71) | | | SUBQ treatment period (through SUBQ day 351) | | |
|------------------------------------------|-------------------------------------------------|---------------------------------------|----------------------------|-------------------------------------------------|--------------------------------------------|----------------------------|
| | SUBQ ravulizumab (<i>n</i> = 84) | IV ravulizumab (<i>n</i> = 45) | Total (<i>N</i> = 129) | SUBQ/SUBQ ravulizumab (<i>n</i> = 84) | IV/SUBQ ravulizumab (<i>n</i> = 44) | Total (<i>N</i> = 128) |
| Asthenia | 3 (3.6) | 0 | 3 (2.3) | 10 (11.9) | 2 (4.5) | 12 (9.4) |
| Anemia | 2 (2.4) | 0 | 2 (1.6) | 8 (9.5) | 2 (4.5) | 10 (7.8) |
| Hemolysis | 1 (1.2) | 1 (2.2) | 2 (1.6) | 5 (6.0) | 3 (6.8) | 8 (6.3) |
| Arthralgia | 1 (1.2) | 1 (2.2) | 2 (1.6) | 5 (6.0) | 2 (4.5) | 7 (5.5) |
| COVID-19 | NR | NR | NR | 11 (13.1) | 7 (15.9) | 18 (14.1) |
| AEs related to study treatment | 31 (36.9) | 7 (15.6) | 38 (29.5) | 31 (36.9) | 10 (22.7) | 41 (32.0) |
| AEs not related to study treatment | 52 (61.9) | 23 (51.1) | 75 (58.1) | 82 (97.6) | 42 (95.5) | 124 (96.9) |
| SAEs related to study treatment | 0 | 0 | 0 | 1 (1.2) | 0 | 1 (0.8) |
| SAEs not related to study treatment | 5 (6.0) | 1 (2.2) | 6 (4.7) | 16 (19.0) | 10 (22.7) | 26 (20.3) |
| Infusion reactions ^d | 38 (45.2) | 8 (17.8) | 46 (35.7) | 46 (54.8) | 16 (36.4) | 62 (48.4) |
| Other serious infections ^e | 1 (1.2) | 0 | 1 (0.8) | 9 (10.7) | 5 (11.4) | 14 (10.9) |

AEs were coded using MedDRA Version 23.1. Patients are counted in each event by relationship to study treatment and severity category in case of multiple events

ADE adverse device effect, *AE* adverse event, *CTCAE* Common Terminology Criteria for Adverse Events, *IV* intravenous, *NA* not applicable, *NR* not reported, *OBDS* on-body delivery system, *SAE* serious adverse event, *SUBQ* subcutaneous

^aADEs are noted as “not applicable” because patients in the IV group did not use the ravulizumab OBDS for SUBQ administration device during the randomized treatment period

^bSeverity of AEs was graded using CTCAE Version 4.03. Grade 1 = mild; grade 2 = moderate; grade 3 = severe; grade 4 = life-threatening; grade 5 = fatal

^cReported in $\geq 5\%$ of all patients during randomized treatment period or SUBQ treatment period; does not include ADEs

^dLocal (infusion site or injection site reactions), systemic (infusion-associated/infusion-related reactions), and immune-mediated (hypersensitivity) reactions

^eIncludes COVID-19, bacterial infections, bacterial sepsis, COVID-19 pneumonia, gastroenteritis, hepatitis viral, salmonellosis, sinusitis, suspected COVID-19, tubo-ovarian abscess

Device Performance and Complaints

The majority (97.6%) of full doses (490 mg) were administered using two ravulizumab OBDS

for SUBQ administration devices. In total, 17,165 devices were used during the study (until the 52-week data cutoff). Full volume per device was delivered by 98.6% of the devices used

during the study. Complaints were reported for 298 of 17,165 device uses attempted (1.7%). The root cause of the reported complaints was use error ($n = 163$), confirmed technical defects ($n = 21$), and unknown defects ($n = 28$); 65 complaints were unable to be analyzed because the device was not returned, and 21 complaints had an ongoing investigation at the time of the data cutoff.

DISCUSSION

In this phase 3 study of patients with PNH who were clinically stable on IV eculizumab, SUBQ ravulizumab achieved PK non-inferiority compared with IV ravulizumab for the primary endpoint of day 71 C_{trough} ($p < 0.0001$). Individual serum free C5 concentrations were less than 0.5 $\mu\text{g/mL}$ in all patients through 1 year of SUBQ administration at all sampling times, demonstrating that complete and sustained terminal complement inhibition comparable with IV ravulizumab was achieved. All efficacy endpoints remained stable over time through 1 year of SUBQ ravulizumab treatment. Full dose SUBQ ravulizumab administration was achieved with the OBDS in almost all administration attempts. The results of this study demonstrate that patients with PNH may be switched from IV eculizumab or IV ravulizumab to SUBQ ravulizumab without loss of efficacy.

The relationship between PK exposure and the clinical effectiveness of IV ravulizumab has previously been established in patients with PNH [12, 13]. With the demonstration of PK non-inferiority of SUBQ ravulizumab to IV ravulizumab in this study, the established efficacy data from IV ravulizumab can be bridged to SUBQ ravulizumab. The complete and sustained C5 inhibition associated with SUBQ ravulizumab may account for the consistent results across endpoints observed in this study.

The safety data indicate that SUBQ ravulizumab administered weekly is well tolerated through at least 1 year of treatment. Overall, the types and incidences of AEs, except for the local injection site reactions, were comparable to those of other IV ravulizumab and IV eculizumab trials, with headache being the most

commonly reported AE [12, 13, 24]. An increased risk of meningococcal infection has been reported in recipients of complement inhibitor therapy [25]. Patients in the trial were vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating the study drug (per protocol) and no such infections were observed.

Treatment-emergent episodes of BTH occurred in five patients through 1 year of SUBQ treatment. Among the five episodes of BTH, four were primarily associated with infection and one was of unknown cause; none of these events were associated with suboptimal C5 inhibition. BTH events caused by complement-amplifying conditions such as infection may occur irrespective of free C5 concentration. Moreover, no MAVE were observed in either treatment group.

FACIT-Fatigue subscale scores were relatively high at baseline (high scores indicate less fatigue), probably because patients enrolled in the study were clinically stable on IV eculizumab prior to study entry. FACIT-Fatigue subscale scores were maintained through the SUBQ treatment period in both groups, suggesting that switching to SUBQ ravulizumab did not affect levels of patient-reported fatigue. Similarly, EORTC QLQ-C30 global health status scores indicated relatively high HRQoL at baseline and remained stable through 1 year of SUBQ ravulizumab treatment. Complementing the HRQoL results, TASQ total scores showed increased satisfaction with the SUBQ route of administration compared with IV eculizumab through 1 year of SUBQ treatment. From a healthcare perspective, SUBQ ravulizumab may reduce time spent receiving therapy, costs, and healthcare resource utilization compared with IV administration [14].

Limitations

There is the potential for bias in an open-label trial design, and the results must be interpreted carefully. Baseline HRQoL and treatment administration satisfaction values were based on eculizumab treatment, which may not reflect current clinical practice because multiple

therapies are now available in this space. Nevertheless, this baseline is consistent with other clinical studies of treatment-experienced patients with PNH [13, 26]. IV ravulizumab is not available in all countries; patients who withdrew from the study in those countries do not have the choice to receive IV ravulizumab, which may have affected their decision to stay on therapy.

CONCLUSIONS

The availability of both IV and SUBQ ravulizumab formulations offers treatment flexibility for patients and physicians. Patients indicated increased satisfaction with the SUBQ route of administration compared with IV eculizumab. With the data for SUBQ ravulizumab demonstrating non-inferiority and a comparable safety profile with IV ravulizumab, the SUBQ method of delivery provides an additional treatment choice for all patients receiving ravulizumab therapy.

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Prior presentation. European Hematology Association 2021 Congress, June 9–17, 2021 and

European Hematology Association 2022 Congress, June 9–12, 2022.

Compliance with Ethics Guidelines. This study was conducted in accordance with the consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines, International Organization for Standardization 14,155 for clinical studies, and applicable laws and regulations. The study protocol and all amendments were reviewed by independent ethics committees at each center, and all patients provided informed consent to participate in the study.

Data Availability. Alexion will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods like 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://alexion.com/our-research/research-and-development>. Link to Data Request Form: <https://alexion.com/contact-alexion/medical-information>.

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