

# Ecilizumab monotherapy for NMOSD: Data from PREVENT and its open-label extension

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**Abstract:** During PREVENT (a phase 3, randomized, double-blind, placebo-controlled, time-to-event study) and its open-label extension (interim analysis), 33 adults with aquaporin-4 immunoglobulin G-positive neuromyelitis optica spectrum disorder (AQP4-IgG + NMOSD) received ecilizumab monotherapy for a median of 2.8 years (range, 14 weeks–5.2 years). At 192 weeks (~4 years), 96% of these patients were free from adjudicated relapses (Kaplan–Meier analysis; 95% confidence interval, 75.7–99.4). During PREVENT, 95% (20/21) of patients receiving ecilizumab monotherapy had no disability worsening. Ecilizumab monotherapy provides effective long-term relapse prevention, relieving the chronic immunosuppression burden in patients with AQP4-IgG + NMOSD. ClinicalTrials.gov; PREVENT: NCT01892345; open-label extension: NCT02003144.

**Keywords:** Clinical trial, neuromyelitis optica (NMO)

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## Introduction

Aquaporin-4 immunoglobulin G-positive neuromyelitis optica spectrum disorder (AQP4-IgG + NMOSD) is an autoimmune central nervous system disorder characterized by relapses leading to accumulating disability.<sup>1</sup> Adverse events (AEs) of chronic immunosuppressive therapy (IST) may limit its tolerability and effectiveness in NMOSD.

Ecilizumab, a humanized monoclonal antibody targeting terminal complement protein C5, was the first approved treatment for AQP4-IgG + NMOSD.<sup>2</sup> In PREVENT, a phase 3, randomized, double-blind, placebo-controlled, time-to-event study (NCT01892345), ecilizumab significantly reduced relapse risk versus placebo (adjudicated relapses: 3.1% vs 42.6% of patients; hazard ratio: 0.058; 95% confidence interval (CI): 0.017–0.197;  $p < 0.0001$ ).<sup>3,4</sup> Ecilizumab was well tolerated, with a safety profile consistent with that in other indications.<sup>3,5–8</sup>

Although permitted, 34 of 143 PREVENT participants received no concomitant IST.<sup>3</sup> All patients receiving ecilizumab monotherapy remained relapse-free at week 96, versus 40% receiving placebo alone.<sup>3</sup>

This report describes ecilizumab monotherapy's long-term efficacy in AQP4-IgG + NMOSD during PREVENT and its open-label extension (OLE; interim analysis; NCT02003144).

## Methods

PREVENT's methodology has been published previously.<sup>3</sup> Briefly: 143 adults were randomized (2:1) to ecilizumab (intravenous maintenance dosage, 1200 mg/2 weeks) or placebo; stable-dose IST was permitted (excluding rituximab and mitoxantrone); patients were vaccinated against *Neisseria meningitidis*.<sup>3</sup> The primary endpoint was time to first adjudicated relapse; PREVENT ended after 23 adjudicated relapses.<sup>3</sup> In total, 119 patients (ecilizumab/ecilizumab, 78; placebo/ecilizumab, 41) received maintenance-dosage ecilizumab in the OLE, with concomitant IST at physician discretion.

We report data from a post hoc analysis (PREVENT and interim OLE: data cutoff, 31 July 2019) of a pre-specified subgroup receiving ecilizumab monotherapy or placebo alone (no concomitant IST) throughout PREVENT and/or the OLE.

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PREVENT/OLE were approved by institutional review boards of participating institutions. All study participants provided written informed consent.

## Results

### Patients

Patient disposition during PREVENT and the OLE is shown in Supplemental Figure S1. In PREVENT, 34 patients received no concomitant IST (eculizumab, 21; placebo, 13); 15 and 12 patients, respectively, entered the OLE. Thirty-three patients receiving eculizumab monotherapy (PREVENT + OLE, 15; PREVENT only, 6; OLE only, 12; Figure 1(a)) were followed up for 87.3 patient-years (PY; median, 2.9 years/patient; range, 23.1–272.1 weeks) and had 85.3 PY of treatment. Eculizumab monotherapy duration was 14.1–271.3 weeks (median, 2.8 years/patient).

Six patients withdrew from PREVENT, and six discontinued the OLE (Supplemental Table S1). At interim data cutoff, 63.6% (21/33) continued to receive monotherapy. Most (69.7%; 23/33) had previously used IST (ceasing 28.9 weeks (median; range, 3.0–707.1 weeks) before PREVENT), and 42.4% (14/33) had previously used rituximab (median, 33.8 weeks (range, 19.6–129.4 weeks) from last dose to PREVENT start). Baseline characteristics are summarized in Table 1.

### Relapses during PREVENT and the OLE

One of 33 patients receiving eculizumab monotherapy experienced an adjudicated relapse (major myelitis (Supplemental Methods), optic spinal impairment scale motor subscale score increase from 1 to 3) after 380 days in the OLE (and 75 days of placebo alone in PREVENT). The adjudicated annualized relapse rate for this group was 0.012 (95% CI: 0.002–0.082) versus 0.625 (95% CI: 0.313–1.250) for the PREVENT placebo alone group ( $n = 13$ ). At 192 weeks of eculizumab monotherapy, 96.2% of patients were free from adjudicated relapses (cumulative probability estimate from Kaplan–Meier analysis, 0.962; 95% CI: 0.757–0.994; Figure 1(b)). Clinical profiles of these 33 patients are summarized in Figure 1(a). No further adjudicated relapses were reported with eculizumab monotherapy through 1 June 2020.

During the OLE, 17/88 patients (19.3%) using concomitant IST at baseline stopped using IST (reasons were not recorded). No adjudicated relapses were reported for these patients during 44.3 weeks (median;

range, 0.3–186.3 weeks) of subsequent eculizumab monotherapy.

### Impact on measures of disability and quality of life during PREVENT

Of 34 patients receiving no concomitant IST throughout PREVENT, 1/21 (4.8%) and 5/13 (38.5%) receiving eculizumab and placebo, respectively, experienced Expanded Disability Status Scale (EDSS) score worsening by PREVENT end (increase  $\geq 2$  from 0,  $\geq 1$  from 1–5, or  $\geq 0.5$  from  $\geq 5.5$  at baseline). Similarly, 1/21 (4.8%) and 4/13 (30.8%) patients, respectively, experienced Hauser Ambulation Index (HAI) score worsening by PREVENT end (increase  $\geq 2$  from 0, or  $\geq 1$  from  $\geq 1$  at baseline).

Between PREVENT baseline and end, mean EDSS and HAI scores improved with eculizumab monotherapy and deteriorated with placebo alone. There were greater improvements in mean modified Rankin scale and EuroQol visual analog scale (EQ VAS) and five-dimension three-level index (EQ-5D-3L) scores with eculizumab monotherapy versus placebo alone (Figure 1(c) and (d)). Improvements in EQ VAS and EQ-5D-3L with eculizumab monotherapy persisted through the OLE (mean (standard deviation (SD)) changes from baseline to interim analysis: 5.9 (17.82) and 0.04 (0.175), respectively).

### Safety

AE and hospitalization rates during eculizumab monotherapy are shown in Supplemental Table S2. The rate of serious infections during PREVENT and the OLE was lower with eculizumab monotherapy (2.3 events/100 PY) than with placebo alone (7.8 events/100 PY). No meningococcal infections or deaths were reported with eculizumab monotherapy through 1 June 2020.

### Discussion

In PREVENT, eculizumab (with/without concomitant IST) reduced relapse risk by 94%.<sup>3,4</sup> PREVENT's design allowed analysis of eculizumab monotherapy over a median of 2.8 years (maximum, 5.2 years) in 33 patients. Although patient numbers were limited, follow-up times ranged widely (23–272 weeks) and analyses were descriptive; these data provide evidence for eculizumab monotherapy's long-term efficacy with a full duration that remains to be determined. At 192 weeks of eculizumab monotherapy, 96% of patients were relapse-free. During PREVENT, 95%

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Supplemental Materials.

of patients receiving ecuzizumab monotherapy had no disability worsening and greater quality of life improvements versus placebo alone; available data

suggested that these quality of life improvements persisted during the OLE. Ecuzizumab monotherapy's long-term safety profile was similar to overall safety

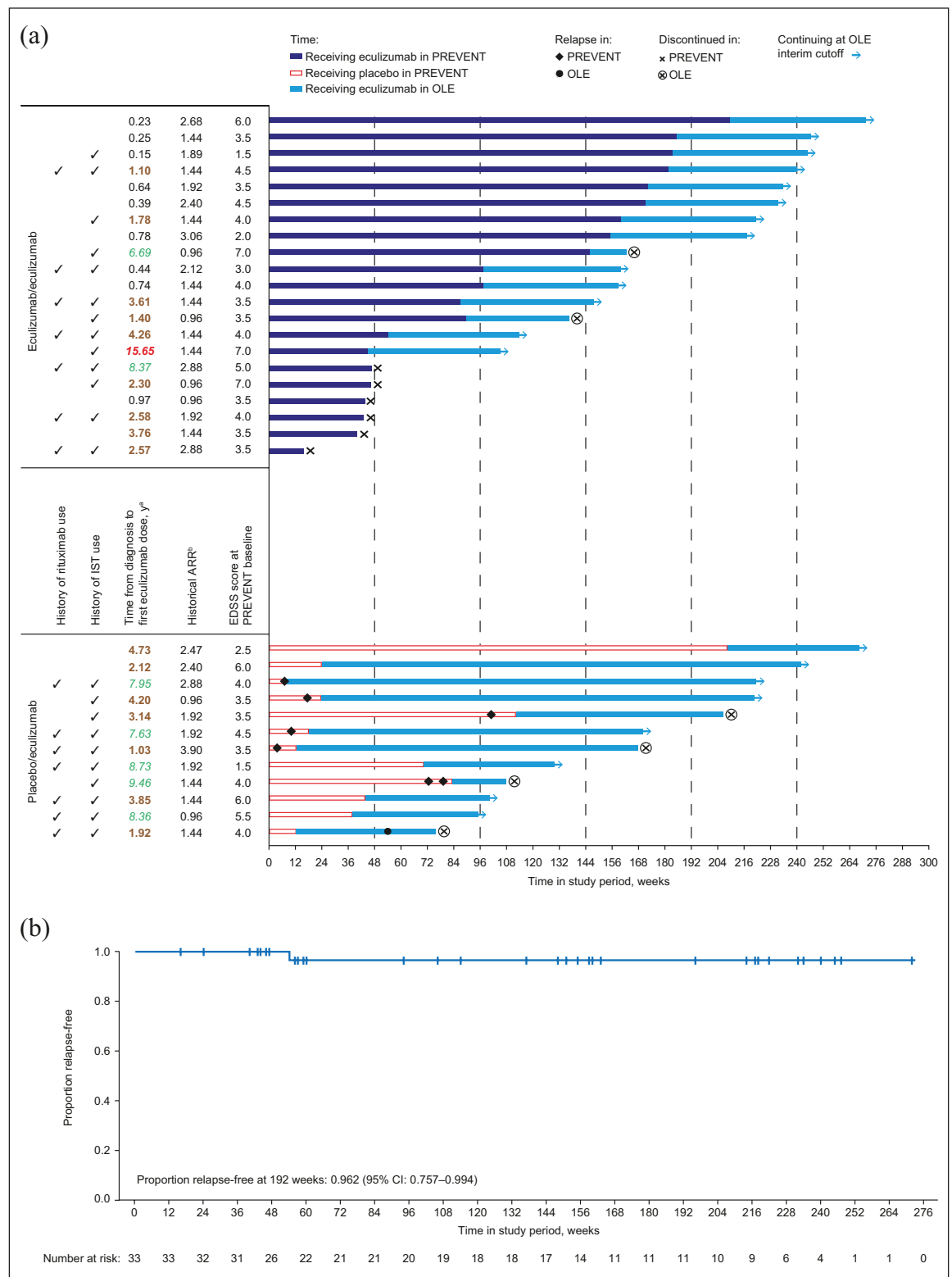
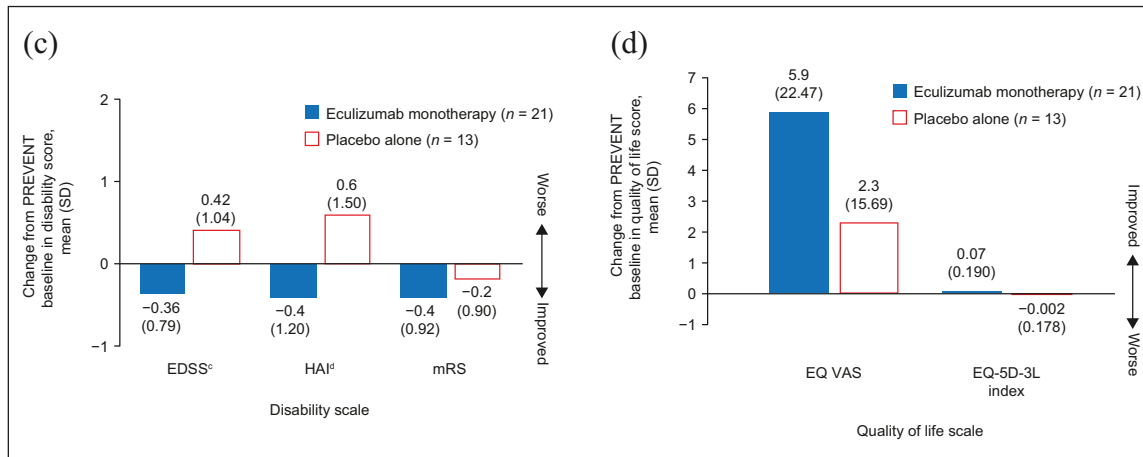


Figure 1. (Continued)



**Figure 1.** Eculizumab monotherapy efficacy outcomes in patients not using concomitant immunosuppressive therapies. (a) Clinical profiles of patients receiving eculizumab monotherapy during PREVENT and OLE ( $n = 33$ ). (b) Time to first adjudicated relapse in patients receiving eculizumab monotherapy during PREVENT and OLE. (c) Changes during PREVENT in mean ( $SD$ ) disability scores by treatment group. (d) Changes during PREVENT in mean ( $SD$ ) quality of life scores by treatment group. Patients who did not experience an adjudicated on-trial relapse were censored at the end of the PREVENT study period (patients who did not enroll in the OLE) or at the OLE interim cutoff date (patients who enrolled in the OLE). The tick marks indicate censoring of data. Proportions of patients who were relapse-free at week 192 were estimated using the Kaplan–Meier product limit method; 95% CI was based on complementary log–log transformation.

Table 1 presents a summary of baseline NMOSD disease characteristics and disease history for this group at eculizumab baseline. One patient in the placebo arm of PREVENT completed the study and did not enroll in the OLE; they were not included in this figure.

<sup>a</sup>0–1 year, black (plain font);  $\geq 1$ –5 years, brown (bold font);  $\geq 5$ –10 years, green (italic font);  $\geq 10$  years, red (bold italic font).

<sup>b</sup>During the 24 months before PREVENT screening.

<sup>c</sup>One patient receiving eculizumab monotherapy experienced EDSS worsening during PREVENT: this patient’s EDSS score was 7.0 at baseline and 7.5 after 1025 days on study; this patient experienced no relapses (adjudicated or physician-determined) during PREVENT.

<sup>d</sup>Another patient receiving eculizumab monotherapy experienced HAI worsening during PREVENT: this patient’s HAI score was 8.0 at baseline and 9.0 after 321 days on study; this patient experienced no relapses (adjudicated or physician-determined) during PREVENT.

ARR: annualized relapse rate; CI: confidence interval; EDSS: Expanded Disability Status Scale; EQ, EuroQol; EQ-5D-3L: EuroQol five-dimension three-level; HAI: Hauser Ambulation Index; IST: immunosuppressive therapy; mRS: modified Rankin scale; NMOSD: neuromyelitis optica spectrum disorder; OLE: open-label extension;  $SD$ : standard deviation; VAS: visual analog scale.

**Table 1.** Baseline demographic characteristics and disease history for patients not using concomitant immunosuppressive therapies.

Variable	PREVENT <sup>a</sup>			PREVENT and OLE <sup>b</sup>
	Eculizumab monotherapy (n = 21)	Placebo alone (n = 13)	All without IST (n = 34)	All eculizumab monotherapy (n = 33)
<b>Sex, n (%)</b>				
Female	20 (95.2)	12 (92.3)	32 (94.1)	31 (93.9)
Male	1 (4.8)	1 (7.7)	2 (5.9)	2 (6.1)
<b>Age at initial clinical presentation, mean (SD), y</b>	30.4 (11.9)	31.5 (10.3)	30.9 (11.2)	30.8 (11.4)
<b>Age at NMOSD diagnosis, mean (SD), y</b>	38.9 (13.6)	33.3 (9.3)	36.7 (12.3)	36.8 (12.5)
<b>NMOSD diagnosis, n (%)</b>				
Definitive NMO	19 (90.5)	11 (84.6)	30 (88.2)	29 (87.9)
NMOSD	2 (9.5)	2 (15.4)	4 (11.8)	4 (12.1)
Longitudinally extensive transverse myelitis	1 (4.8)	2 (15.4)	3 (8.8)	3 (9.1)
Optic neuritis	1 (4.8)	0 (0.0)	1 (2.9)	1 (3.0)

(Continued)

**Table 1.** (Continued)

Variable	PREVENT <sup>a</sup>			PREVENT and OLE <sup>b</sup>
	Eculizumab monotherapy ( <i>n</i> = 21)	Placebo alone ( <i>n</i> = 13)	All without IST ( <i>n</i> = 34)	All ecilizumab monotherapy ( <i>n</i> = 33)
<b>Historical ARR (in the 24 months before PREVENT screening), mean (<i>SD</i>)</b>	1.8 (0.67)	1.9 (0.82)	1.8 (0.73)	1.8 (0.73)
<b>Historical relapse type (in the 24 months before PREVENT screening), <i>n</i> (%)</b>				
Optic neuritis	17 (81.0)	5 (38.5)	22 (64.7)	22 (66.7)
Transverse myelitis	17 (81.0)	13 (100.0)	30 (88.2)	29 (87.9)
Brain-stem symptoms	6 (28.6)	5 (38.5)	11 (32.4)	11 (33.3)
Cerebral symptoms	4 (19.0)	2 (15.4)	6 (17.6)	6 (18.2)
Other symptoms	7 (33.3)	4 (30.8)	11 (32.4)	11 (33.3)
<b>Prior IST use (before PREVENT baseline), <i>n</i> (%)</b>	13 (61.9)	11 (84.6)	24 (70.6)	23 (69.7)
Azathioprine	7 (33.3)	5 (38.5)	12 (35.3)	11 (33.3)
Corticosteroids	6 (28.6)	4 (30.8)	10 (29.4)	9 (27.3)
Cyclophosphamide	2 (9.5)	0 (0.0)	2 (5.9)	2 (6.1)
Intravenous immunoglobulin	0 (0.0)	1 (7.7)	1 (2.9)	0 (0.0)
Methotrexate	2 (9.5)	2 (15.4)	4 (11.8)	3 (9.1)
Mitoxantrone or cladribine	2 (9.5)	2 (15.4)	4 (11.8)	4 (12.1)
Mycophenolate mofetil	4 (19.0)	3 (23.1)	7 (20.6)	7 (21.2)
Rituximab (>3 months before screening)	7 (33.3)	7 (53.8)	14 (41.2)	14 (42.4)
<b>EDSS score</b>				
Mean ( <i>SD</i> )	4.2 (1.5)	4.0 (1.3)	4.1 (1.4)	4.2 (1.8)
Median (range)	4.0 (1.5–7.0)	4.0 (1.5–6.0)	4.0 (1.5–7.0)	4.0 (0.0–7.0)
<b>HAI score</b>				
Mean ( <i>SD</i> )	2.3 (2.6)	2.0 (1.0)	2.2 (2.1)	2.6 (2.4)
Median (range)	1.0 (0–8.0)	2.0 (1.0–4.0)	2.0 (0–8.0)	2.0 (0–8.0)
<b>mRS score</b>				
Mean ( <i>SD</i> )	2.3 (1.1)	2.1 (1.0)	2.2 (1.0)	2.3 (1.3)
Median (range)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (0–6.0)
<b>EQ VAS score, mean (<i>SD</i>)</b>	62.3 (20.9)	58.1 (22.0)	60.7 (21.1)	63.7 (20.9)
<b>EQ-5D-3L index score, mean (<i>SD</i>)</b>	0.64 (0.24)	0.68 (0.20)	0.66 (0.23)	0.66 (0.22)

ARR: annualized relapse rate; EDSS: Expanded Disability Status Scale; EQ, EuroQol; EQ-5D-3L: EuroQol five-dimension three-level; HAI: Hauser Ambulation Index; IST: immunosuppressive therapy; mRS: modified Rankin scale; NMO: neuromyelitis optica; NMOSD: neuromyelitis optica spectrum disorder; OLE: open-label extension; *SD*: standard deviation; VAS: visual analog scale; y: year.

<sup>a</sup>PREVENT baseline.

<sup>b</sup>Eculizumab baseline (PREVENT baseline for patients who received ecilizumab during PREVENT; PREVENT OLE baseline for those who received placebo during PREVENT and enrolled in the OLE).

observations during PREVENT; notably, the rate of serious infections was low. Further research and clinical reports of ecilizumab monotherapy are necessary to confirm these findings.

Efficacy data for other novel therapies without concomitant ISTs in AQP4-IgG + NMOSD have been published, and further data are needed for comparison because of study differences in patients and relapse definitions. In summary, relapse risk reductions in patients with AQP4-IgG + NMOSD have been

reported for satralizumab monotherapy versus placebo alone (83% and 55% relapse-free after 48 weeks, respectively; *n* = 64)<sup>9</sup> and inebilizumab monotherapy versus placebo alone (88% and 57% relapse-free after 28 weeks, respectively; *n* = 213).<sup>10</sup> In PREVENT, 100% and 61% of patients remained relapse-free after 48 weeks of ecilizumab monotherapy and placebo alone, respectively (*n* = 34).<sup>3</sup>

In conclusion, these findings provide evidence for effective long-term management of AQP4-IgG +

NMOSD with eculizumab monotherapy, avoiding the use of off-label IST. This may be particularly valuable for patients at increased risk of AEs and those intolerant of IST.

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### Author Contributions

S.J.P., S.S., L.M., and R.A. contributed to the concept and design of the study. All authors contributed to the acquisition, analysis, or interpretation of data, and to drafting/critical revision of the manuscript for important intellectual content and final approval of the manuscript. PREVENT study group members who provided and cared for study patients in this subgroup and collected data from them are listed as study collaborators in the Supplemental Materials.

### Declaration of Conflicting Interests

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### Data Availability Statement


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 <http://alexion.com/our-research/research-and-development>. Link to data request form: <https://alexion.com/contact-alexion/medical-information>

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### Supplemental Material

Supplemental material for this article is available online.

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