

ICD-10 PROCEDURE CODE PRESENTATION

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DISCLAIMER

- S. Chloe Sader is a full-time employee of Alexion Pharmaceuticals, Inc.

BACKGROUND

- Alexion Pharmaceuticals submitted a New Technology Add-on Payment (NTAP) for Soliris when used in Neuromyelitis Optica Spectrum Disorder (NMOSD) on October 11, 2019.
- There is no current procedure code that uniquely identifies the administration of Soliris to patients with NMOSD.
- Therefore, Alexion respectfully requests that CMS assign a new ICD-10 procedure for the administration of Soliris in NMOSD patients to complement the NTAP application.

NMOSD: DISEASE OVERVIEW

- **Description**

- Rare and severe autoimmune disease that attacks the central nervous system without warning footnotes 1 through 3

- **Epidemiology**

- The incidence of NMOSD in the US is 0.7/100,000, while the prevalence is 3.9/100,000 footnote 4
- 83% of cases are female, and median onset occurs at 39 years of age footnote 5, footnote 6

- **Biomarker**

- The AQP4 antibody, which targets the aquaporin 4 water channel in the CNS, was identified as a specific biomarker for NMOSD that helps determine definitive diagnosis footnote 7 through 9

Abbreviations: AQP4, aquaporin 4; NMOSD, neuromyelitis optica spectrum disorder.

Sources: Footnote 1. Kitley J, et al. *Brain* 2012; 135:1834–1849. Footnote 2. Mutch K, et al. *Disabil Rehabil*. 2014; 36(13):1100–1107. Footnote 3. Wingerchuk DM, et al. *Neurology* 2003; 60(5):848-853. Footnote 4. Flanagan EP, et al. *Ann Neurol*. 2016; 79(5):775-783. Footnote 5. Bukhari W, et al. *J Neurol Neurosurg Psychiatry*. 2017; 88(8):632-638. Footnote 6. Wingerchuk DM, et al. *Lancet Neurol*. 2007; 6:805-815. Footnote 7. Lennon VA, et al. *Lancet* 2004; 364:2106-2112. Footnote 8. Isobe N, et al. *Mult Scler*. 2012; 18(11):1541-1551. Footnote 9. Lennon VA, et al. *J Exp Med*. 2005; 202(4):473-477.



JOURNEY TO THE FIRST FDA-APPROVED THERAPY FOR PATIENTS WITH NMOSD

- 1894: Devic's Disease presentation ^{footnote 1}
- 1999: Wingerchuk NMO Criteria ^{footnote 2}
- 2002: Role of complement in NMO first described in literature ^{footnote 3}
- 2004: Aquaporin-4 antibodies (AQP4-IgG) discovered ^{footnote 4, footnote 5}
- 2006: Revised Wingerchuk Diagnostic Criteria ^{footnote 5, footnote 6}
- 2007: *Soliris approved for PNH*
- **2009: NMOSD open-label pilot study**
- 2011: *Soliris approved for aHUS*
- **2014: NMOSD PREVENT clinical trial**
- 2015: IPND Revised Diagnostic Criteria ^{footnote 7}
- 2017: *Soliris approved for anti-AChR+gMG*
- **2019: *Soliris approved in AQP4+ NMOSD***



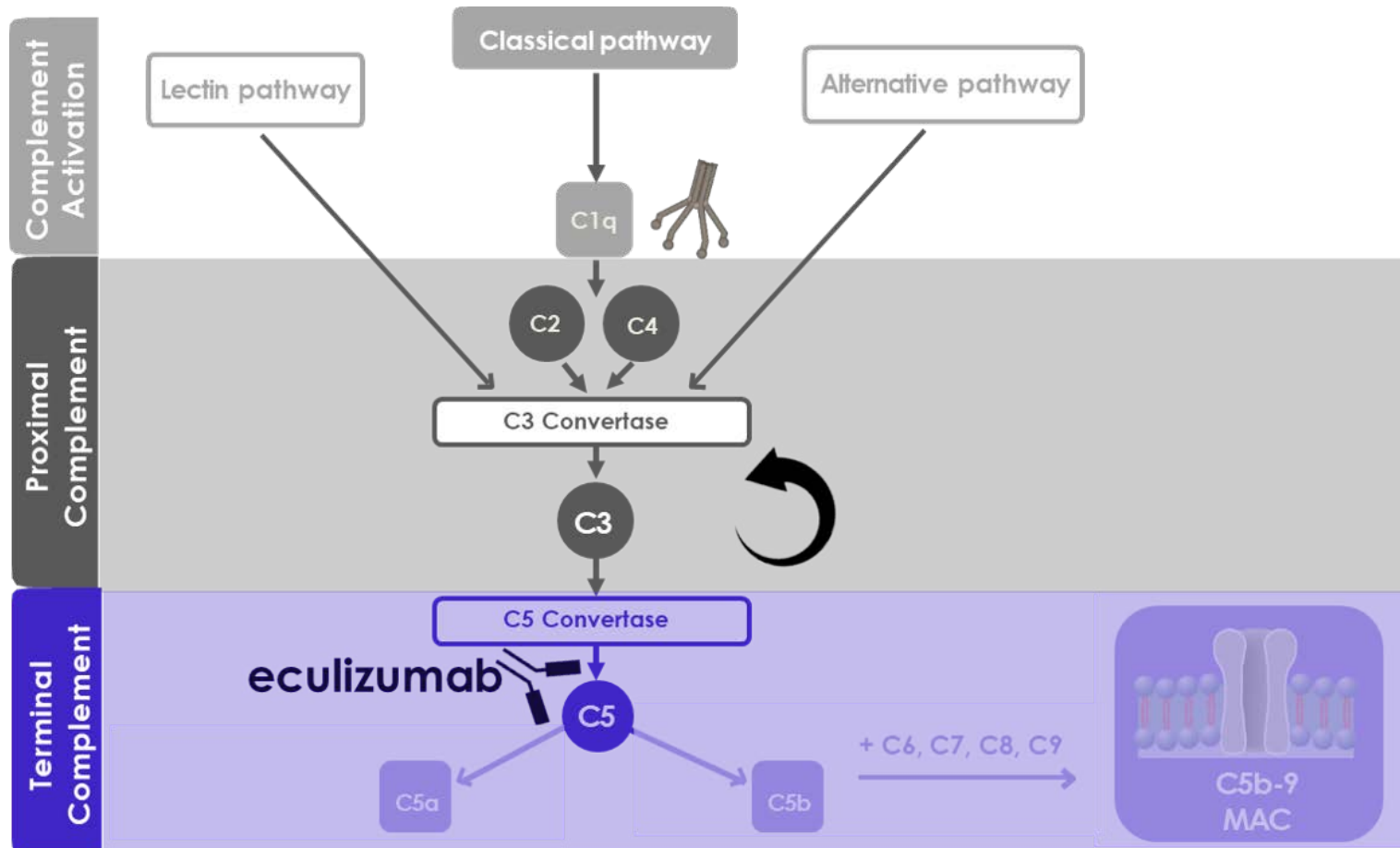
Soliris is the first-ever FDA-approved therapy for NMOSD in adult patients who are anti-AQP4 antibody positive

Abbreviations: AChR, acetylcholine receptor; aHUS, atypical hemolytic uremic syndrome; FDA, Food and Drug Administration; gMG, generalized myasthenia gravis; LETM, longitudinal extensive transverse myelitis; MRI, magnetic resonance imaging; ON, optic neuritis; PNH, paroxysmal nocturnal hemoglobinuria; TM, transverse myelitis.

Sources: Footnote 1. Jarius S. *J Neuroinflammation*. 2013;10:8. Footnote 2. Wingerchuk DM, et al. *Neurology*. 1999;53(5):1107-1114. Footnote 3. Lucchinetti CF, et al. *Brain*. 2002;125(Pt 7):1450-1461. Footnote 4. Weinshenker BG, et al. *Mayo Clin Proc*. 2017;92(4):663-679. Footnote 5. Wingerchuk DM, et al. *Lancet Neurol*. 2007;6(9):805-815. Footnote 6. Wingerchuk DM. *Neurology*. 2006;66(10):1485-1489. Footnote 7. Wingerchuk DM, et al. *Neurology*. 2015;85(2):177-189.



SOLIRIS® (ECULIZUMAB) BINDS C5 AND INHIBITS THE TERMINAL COMPLEMENT PATHWAY FOOTNOTES 1 THROUGH 4



- The Complement pathway is activated by the:
 - **Classical Pathway** – activates C1q via binding of antigen:antibody complexes (eg, AQP4 autoantibodies)
 - Lectin Pathway – activated by bacterial cell walls
 - Alternative pathway – activation of C3
- Key functions of Proximal Complement ^{footnote 3}
 - C1q activates C3 convertase, which increases C3
 - Immune complex clearance
 - Microbial opsonization
 - Inflammation
- Eculizumab blocks key functions of terminal complement ^{footnote 3, footnote 4}
 - Inflammation caused by C5a
 - Formation of MAC resulting from C5b
 - Direct cell lysis
 - Astrocyte damage (in anti-AQP4+ NMOSD)

Abbreviations: MAC, membrane attack complex.

Sources: Footnote 1. Soliris (eculizumab) Prescribing Information. Alexion Pharmaceuticals, Inc. June 2019. Footnote 2. Walport MJ. *N Engl J Med*. 2001;344(14):1058-1066. Footnote 3. Rother RP, et al. *Nat Biotechnol*. 2007;25(11):1256-1264. Footnote 4. Dutra BG, et al. *Radiographics*. 2018;38(1):169-193.

PATHOPHYSIOLOGY OF AQP4-IgG-POSITIVE NMOSD

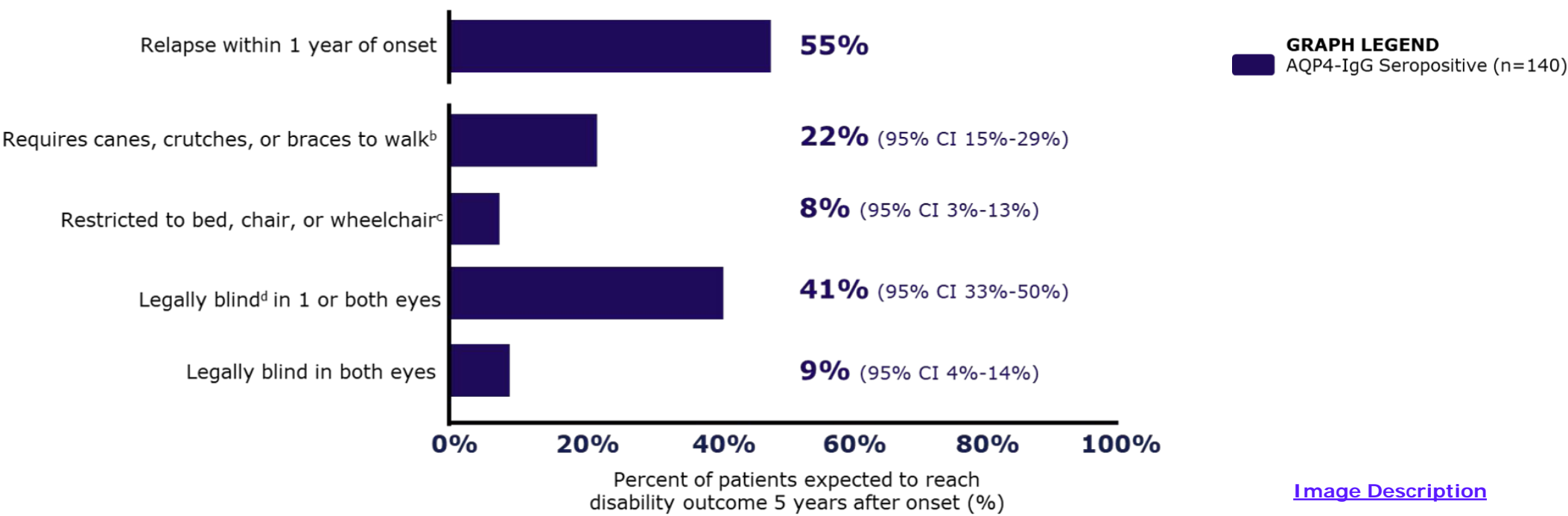
FOOTNOTE 1, FOOTNOTE a

1. AQP4-IgG accesses central nervous system through the blood brain barrier
2. Anti-AQP4 autoantibodies cause complement activation
3. Leukocyte infiltration and degranulation occurs
4. Damage occurs to astrocytes leading to astrogliopathy
5. Loss of other cells and demyelination occurs

5-YEAR PROGNOSIS OF PATIENTS WITH AQP4-IgG SEROPOSITIVE NMOSD

Footnotes a through d

Kaplan-Meier estimate of % of patients expected to reach disability outcome 5 years after onset



Abbreviations: EDSS, Expanded Disability Status Scale.
Footnote a Data from retrospective study of 163 patients (140 seropositive, 23 seronegative) with NMOSD identified from Mayo Clinic records from 2005-2011. The relapse rates were compared between intervals with and without therapy using linear regression models with generalized estimating equations. Disability and blindness outcomes were compared between groups using log-rank tests, and the risk of these outcomes was estimated using the Kaplan-Meier method. Adjusted associations of patient characteristics with these outcomes were assessed with Cox proportional hazards regression models. Footnote b EDSS ≥6: Intermittent/unilateral assistance (canes, crutches, or braces) required to walk 100 m with/without resting or worse. Footnote c EDSS ≥8: Restricted to bed/chair or perambulated in wheelchair but may be out of bed much of day, retains many self-care functions, generally has effective use of arms or worse. Footnote d Sustained visual acuity of 20/200 or less with best correction possible for more than 6 months.
Source: Jiao Y, et al. *Neurology*. 2013;81(14):1197-1204.

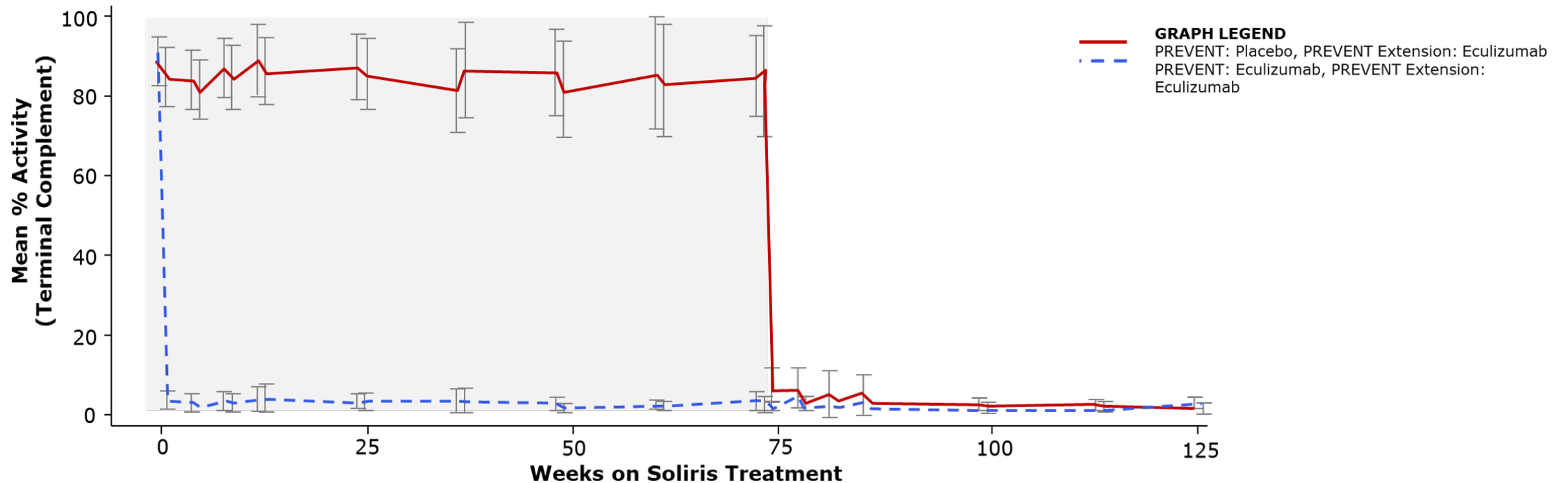
CURRENT MANAGEMENT GOALS AND TREATMENT PRACTICES

- Management goals in NMOSD ^{footnote 1}:
 - Relapse prevention therapy — neuroprotection and to prevent accrual of disability
 - Symptomatic therapy — to help manage residual symptoms
- In the absence of FDA-approved therapies, off-label agents have been used to treat NMOSD, although data are limited to case series and retrospective cohort studies ^{footnotes 2 through 6}

Soliris is the first-ever FDA-approved therapy for NMOSD in adult patients who are anti-AQP4 antibody positive ^{footnote 7}

ECULIZUMAB RAPIDLY INHIBITS THE TERMINAL COMPLEMENT PATHWAY

Mean Terminal Complement Activity During PREVENT and PREVENT Extension

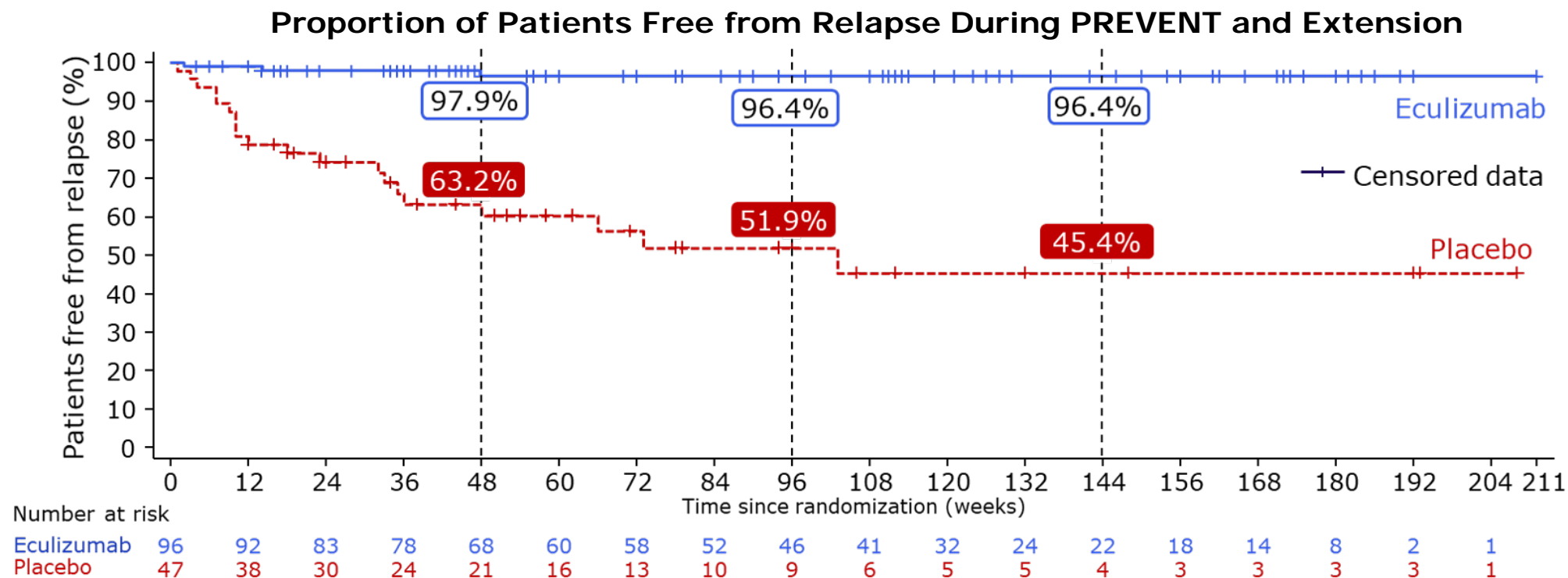


[Image Description](#)

- PREVENT data shown until week 72 (shaded region)
- Error bars represent 95% CI based on standard error of mean



SOLIRIS® (ECULIZUMAB)-TREATED PATIENTS EXPERIENCED A 94% RELATIVE RISK REDUCTION COMPARED TO PATIENTS ON PLACEBO FOOTNOTE 1, FOOTNOTE 2, FOOTNOTE a



[Image Description](#)

- The time to the first adjudicated on-trial relapse was significantly longer in eculizumab-treated patients compared to placebo-treated patients ($p < 0.0001$) Footnote 1, Footnote 3
- Median time to first adjudicated relapse: not reached (eculizumab) vs. 103 weeks (placebo)
- Hazard ratio Footnote b for relapse was 0.06 (95% CI, 0.02 to 0.20), representing a 94.2% reduction in the risk of relapse ($p < 0.001$) Footnote c
- Proportion relapse-free at 48 weeks (95% CI) Footnote 3:
 - Eculizumab: 0.979 (0.918, 0.995)

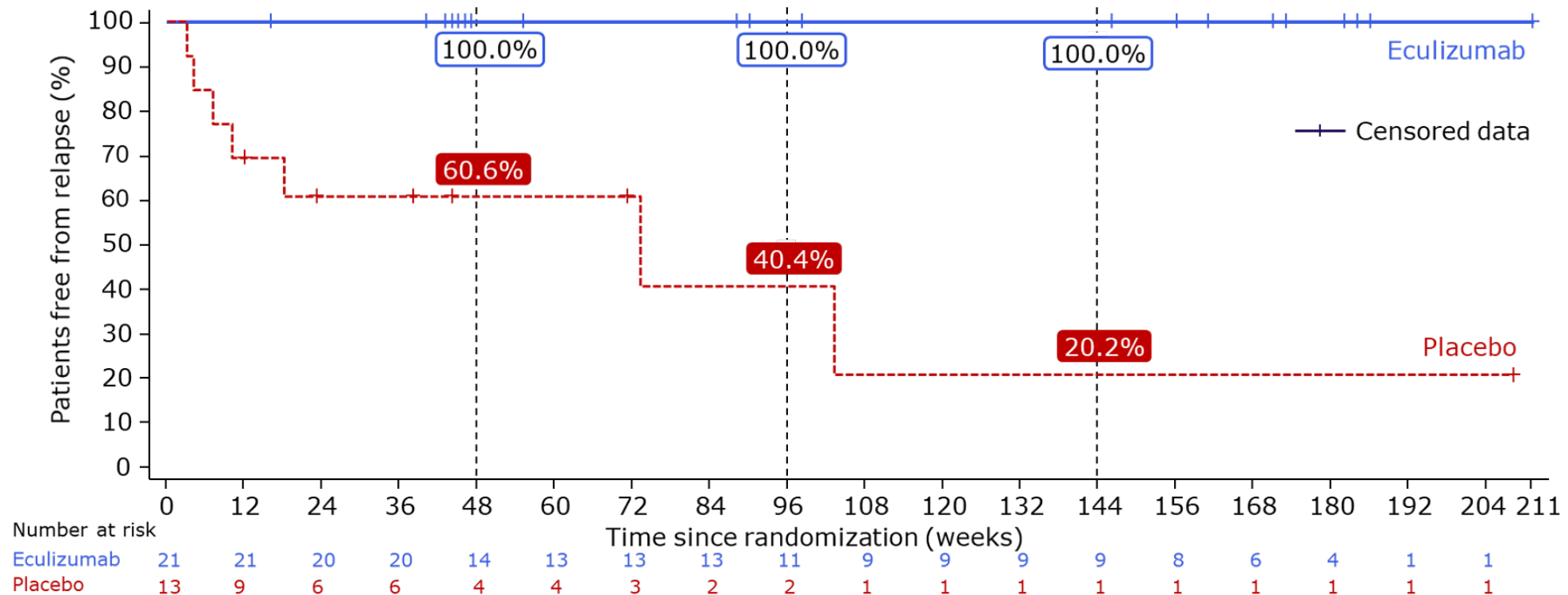
Footnote a Patients who did not experience an adjudicated on-trial relapse were censored at the end of the study period. Footnote 1 Footnote b Based on a stratified Cox proportional hazards model. Footnote 2 Footnote c Based on a stratified log-rank test. Footnote 2

Source: Footnote 1. Pittock SJ, et al. *N Engl J Med*. 2019;381(7):614-625. Footnote 2. Pittock SJ, et al. Presented at: American Academy of Neurology Annual Meeting. May 4-10, 2019. Philadelphia, PA. Footnote 3. Data on file. Alexion Pharmaceuticals, Inc.



100% OF PATIENTS WHO RECEIVED SOLIRIS® (ECULIZUMAB) AS MONOTHERAPY WERE RELAPSE-FREE AT APPROXIMATELY 1 YEAR

Proportion of Patients free from Relapse During PREVENT



[Image Description](#)



SOLIRIS® (ECULIZUMAB) REDUCED HOSPITALIZATIONS AND USE OF RESCUE THERAPY

- Compared to placebo, patients treated with Soliris had reduced annualized rates of:

Metric	Hospitalizations	Acute Relapse Treatments: Corticosteroids	Acute Relapse Treatments: Plasma Exchange
Relative reduction compared to placebo, (%)	87	83	90
Soliris ARR	0.04	0.07	0.02
Placebo ARR	0.31	0.42	0.19

SAFETY SUMMARY OF SOLIRIS® (ECULIZUMAB) IN PATIENTS WITH AQP4- IgG-POSITIVE NMOSD Footnote 1, Footnote a

ECULIZUMAB-TREATED (n = 96)

SAFETY PROFILE

AEs	Events, n	Events/100 patient-years	Patients, n (%)
Any AE	1288	745	88 (92)
Any SAE	46	27	25 (26)
Death	1	1	1 (1) footnote b
Meningococcal infection	0	0	0
AE leading to discontinuation of agent footnote c	0	0	0 (0.0)
URTI footnote d	54	31	28 (29)
Headache footnote d	95	55	22 (23)
Nasopharyngitis footnote d	50	29	20 (21)
Nausea footnote d	30	17	16 (17)
Diarrhea footnote d	23	13	15 (16)
Urinary tract infection footnote d	45	26	13 (14)
Limb pain footnote d	13	8	11 (11)
Vomiting footnote d	10	6	10 (10)

PLACEBO-TREATED (n = 47)

SAFETY PROFILE

AEs	Events, n	Events/100 patient-years	Patients, n (%)
Any AE	599	1127	43 (91)
Any SAE	29	55	13 (28)
Death	0	0	0 (0.0)
Meningococcal infection	0	0	0
AE leading to discontinuation of agent footnote c	3	6	2 (4)
URTI footnote d	10	19	6 (13)
Headache footnote d	20	38	11 (23)
Nasopharyngitis footnote d	15	28	9 (19)
Nausea footnote d	19	36	12 (26)
Diarrhea footnote d	19	36	7 (15)
Urinary tract infection footnote d	13	24	10 (21)
Limb pain footnote d	11	21	10 (21)
Vomiting footnote d	10	19	8 (17)

Abbreviations: AE, adverse event; SAE, serious adverse event; URTI, upper respiratory tract infection.

Footnote a Data exclude events of NMOSD that were relapses meeting the definition of a serious AE. Footnote b The patient died from infectious pleural effusion (reported as pulmonary empyema), which the investigator categorized as probably related to the trial agent. The associated cultures yielded *Streptococcus intermedius* and *Peptostreptococcus micros*, and the patient had an extensive history of pulmonary disease (including bronchiolitis obliterans requiring tracheostomy, pneumonia, asthma, and obstructive sleep apnea) and was an active smoker. Footnote c Two patients discontinued placebo due to adverse events of pneumonia in one patient and pre-renal failure & pancytopenia in the other patient. Footnote d AEs reported in 15% or more in either arm

Sources: Footnote 1. Pittock SJ, et al. *N Engl J Med*. 2019;381(7):614-625. Footnote 2. Soliris (eculizumab) Prescribing Information. Alexion Pharmaceuticals, Inc. June 2019.



SOLIRIS® (ECULIZUMAB) MENINGOCOCCAL RISK

- Soliris has a Boxed WARNING for risk of serious meningococcal infections. Life-threatening and fatal meningococcal infections have rarely occurred in patients treated with Soliris and can be mitigated with proper vaccination
- Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS, prescribers must enroll in the program

PREPARATION AND RECONSTITUTION OF SOLIRIS®

Soliris Dose	Diluent Volume	Final Volume
300 mg	30 mL	60 mL
600 mg	60 mL	120 mL
900 mg	90 mL	180 mL
1200 mg	120 mL	240 mL