

Drug Class Review with New Drug Evaluation: Biologics for Autoimmune Disorders-Neuromyelitis Optica Spectrum Disorder

Date of Review: April 2021

Generic Name:

Eculizumab

Inebilizumab-cdon

Satralizumab-mwge

Date of Last Review: n/a

Dates of Literature Search: 1/1/1996 – 1/20/2021

Brand Name (Manufacturer):

Soliris® (Alexion Pharmaceuticals)

Uplizna™ (Vielia Bio)

Enspryng™ (Genentech/Roche)

Dossiers Received: Yes

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

To define place in therapy for 3 immunosuppressive agents, eculizumab, inebilizumab-cdon, and satralizumab-mwge, recently approved by the Food and Drug Administration (FDA) for the treatment adults with neuromyelitis optica spectrum disorder (NMOSD).

Research Questions:

1. What is the effectiveness of eculizumab, inebilizumab, and satralizumab in reducing time to relapse in adult patients with NMOSD who are anti-aquaporin-4 (AQP4) antibody positive?
2. What are the harms of eculizumab, inebilizumab-cdon and satralizumab in adults with NMOSD?
3. Is there comparative evidence that eculizumab, inebilizumab, and satralizumab differ in efficacy or harms for management of NMOSD?
4. Are there certain sub-populations (based on age, gender, ethnicity, comorbidities, disease duration or severity) in which eculizumab, inebilizumab, or satralizumab may be beneficial or cause more harm?

Conclusions:

Eculizumab

- A phase 3, double-blind, time-to-event, multicenter trial evaluated the safety and efficacy of eculizumab in adults (n=143) with highly active AQP4-IgG seropositive NMOSD.¹ In the PREVENT trial, eculizumab was primarily add-on therapy, 78% of patients at baseline were receiving a stable-dose regimen of immunosuppressive therapy (IST) including chronic corticosteroids.¹ The primary end point was the number of adjudicated initial relapses compared to placebo.¹ Moderate quality evidence shows adjudicated relapses occurred in 3% of subjects in the eculizumab group and 43% of subjects in the placebo group (hazard ratio [HR], 0.06; 95% confidence interval [CI], 0.02 to 0.20; P<0.001; Number Needed to Treat [NNT] 3) over the follow-up period (median

follow-up period: 90 weeks for active drug and 43 weeks for placebo).¹ A significant reduction in adjudicated annualized relapse rate was observed in patients treated with eculizumab compared with placebo (0.02 in the eculizumab group vs. 0.35 in the placebo group rate ratio [RR], 0.045; 95% CI, 0.013 to 0.151; P<0.0001).¹ The mean change in the Expanded Disability Scale Score (EDSS) score (range 0 to 10) from baseline was not significantly different between the 2 treatment arms (-0.18 in the eculizumab group and 0.12 in the placebo group; least-squares mean difference [LSMD], -0.29; 95% CI, -0.59 to 0.01).¹ The median change in EDSS was 0 for both treatment groups, and over 70% of eculizumab-treated patients had the same or experienced worsening of their EDSS scores at the end of study assessment.²

- Eculizumab prescribing information contains a black box warning due to an increased risk of life-threatening and fatal meningococcal infections which was identified in initial trials evaluating eculizumab use in indications other than NMOSD.³ Healthcare providers who prescribe eculizumab must enroll in the Solaris[®] Risk Evaluation and Mitigation Strategy (REMS) restricted program.³
- In the PREVENT trial, upper respiratory tract infections (29% vs. 13%), nasopharyngitis (21% vs. 19%), back pain (16% vs. 15%), and dizziness (15% vs. 13%) were more common in the eculizumab group compared with the placebo group.¹

Inebilizumab

- N-MOMentum was a phase 2/3 double-blind trial that evaluated the safety and efficacy of inebilizumab as monotherapy in reducing the risk of relapse and disability in adults with AQP4 seropositive or seronegative NMOSD. Ninety-three percent (n=213) of enrolled subjects were AQP4 seropositive.⁴ The primary endpoint was to compare the efficacy of inebilizumab with placebo in reducing the risk of NMOSD attack in patients.⁴ Moderate-quality evidence showed 12% of 174 participants receiving inebilizumab in the intention-to-treat (ITT) population had an attack versus 39% of 56 participants receiving placebo (hazard ratio (HR) 0.272; 95% CI 0.150 to 0.496; p<0.0001; NNT 4) before day 197 of the trial.⁴ In the AQP4 seropositive population, 11% of patients receiving inebilizumab had an attack compared with 42% of patients receiving placebo treatment (HR 0.227; 95% CI 0.121 to 0.423; p<0.0001; NNT 4).⁴ Among the 17 AQP4-seronegative patients who were randomly allocated to treatment (13 to inebilizumab), three attacks occurred, all in the inebilizumab group.⁴ Because only four AQP4-seronegative patients were randomly allocated to placebo and no attack occurred in this group, inebilizumab efficacy could not be interpreted in the AQP4-seronegative cohort.⁴
- Across both the randomized and open-label treatment in the N-MOMentum trial, the most common adverse reactions (greater than or equal to 10%) were urinary tract infection (20%), nasopharyngitis (13%), infusion reaction (12%), arthralgia (11%), and headache (10%).⁵ Inebilizumab can cause infusion reactions, which can include headache, nausea, somnolence, dyspnea, fever, myalgia, or rash.⁵ During the randomized clinical trial period, infusion reactions were observed with the first course of inebilizumab in 9% of AQP4 seropositive NMOSD patients and 10% of patients in the placebo arm.⁵ Premedication with IV methylprednisolone 80 mg to 125 mg, oral diphenhydramine 25 mg to 50 mg and oral acetaminophen 500 mg to 650 mg is recommended prior to each infusion to reduce the frequency and severity of infusion reactions.⁵

Satralizumab

- The safety and efficacy of satralizumab in NMOSD patients were evaluated in two phase 3, randomized, placebo-controlled, multicenter, double-blinded studies with open-label extensions.^{6,7} In both studies, the primary endpoint was evaluated in the ITT population, consisting of both AQP4 seropositive and AQP4 seronegative patients, and measured the time to first protocol-defined relapse (PDR).^{6,7} SAKuraSky⁶ investigated satralizumab added to baseline IST in adolescents and adults (n=83), while SakuraStar⁷ evaluated satralizumab monotherapy in adults (n=95). Enrollment of AQP4 seronegative patients was limited to 30% in both trials to reflect estimated prevalence in the NMOSD population.
- Moderate-quality evidence from the SAKuraSky trial showed that among patients who received satralizumab, 20% (n=8) experienced a PDR compared with 43% (n=18) of patients who received placebo (HR 0.38; 95% CI, 0.16 to 0.88; p=0.02; NNT 5).⁶ In AQP4-IgG seropositive patients, 11% of satralizumab-treated

patients experienced a PDR at week 48 compared with 43% of placebo-treated patients (HR=0.66; 95% CI: 0.06-0.75; p=0.0086; moderate quality evidence).⁶ Two key quality of life (QoL) secondary end points were the change from baseline to week 24 in the visual-analogue scale (VAS) pain score (range, 0 to 100, with higher scores indicating more pain) and the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) score (range, 0 to 52, with lower scores indicating more fatigue). There were no significant differences in pain or fatigue reported between treatment groups.⁶

- In the SakuraStar trial, moderate quality evidence showed that relapses occurred in 19 (30%) patients receiving satralizumab and 16 (50%) receiving placebo (HR 0.45, 95% CI, 0.23 to 0.89; p=0.018, NNT 5).⁷ In AQP4-IgG seropositive patients, satralizumab showed a 74% reduction in the risk of relapse (HR=0.26; 95% CI: 0.11 to 0.63; moderate quality evidence).⁷ The key secondary QoL outcome measures, change in baseline pain on the VAS and functional assessment of chronic fatigue on the FACIT-F scores, were not significantly different between treatment groups.⁷
- The most common risks of treatment with satralizumab were an increased risk of several types of infections (nasopharyngitis, upper respiratory tract infection), headache, rash, arthralgia, extremity pain, fatigue, and nausea. Other IL-6 antagonists (sarilumab and tocilizumab) have boxed warnings for serious infections and potential tuberculosis or hepatitis B reactivation.⁸

Biologics for NMOSD

- No head-to-head trials have provided comparative evidence that eculizumab, inebilizumab, and satralizumab may differ in efficacy or harms for management of NMOSD. There is insufficient comparative evidence to evaluate functional status, quality of life, and disability.
- There is insufficient evidence to demonstrate specific sub-populations (based on age, gender, ethnicity, comorbidities, disease duration or severity) may have more benefit or reduced harm with eculizumab, inebilizumab, or satralizumab.

Recommendations:

- Create a new class of drugs on the PDL entitled “Biologics for Rare Diseases” and include eculizumab, inebilizumab, satralizumab in this new class.
- Implement clinical prior authorization (PA) criteria for each biologic agent to ensure appropriate utilization in FDA-approved indications funded by Oregon Health Plan (**Appendix 4**).
- After evaluation of costs in executive session, make eculizumab non-preferred and make satralizumab and inebilizumab preferred.

Background:

NMOSD or Devic’s disease, is a rare, autoimmune, severe demyelinating disease of the central nervous system that predominantly involves inflammation of the optic nerve and spinal cord.⁹ The pathogenesis is unknown, but it appears to be related to B-cell autoimmunity directed against aquaporin-4, the dominant water channel in the central nervous system. Features of NMOSD include acute attacks of rapidly sequential optic neuritis (leading to severe visual loss) or transverse myelitis (often causing limb weakness, sensory loss, and bladder dysfunction) with a typically relapsing course.⁹ Neuromyelitis optica had long been considered a subtype of multiple sclerosis (MS) due to the similarities between the clinical presentations of MS and NMOSD.¹⁰ However, recent evidence indicates NMOSD is usually associated with a specific biomarker, aquaporin-4 immunoglobulin-G (AQP4-IgG) antibody, which differentiates NMOSD from MS.¹¹ In the central nervous system aquaporins maintain neuroexcitatory processes and water homeostasis between the blood, cerebrospinal fluid and brain parenchyma.¹² Anti-AQP4-IgG antibodies trigger the complement cascade, which leads to inflammation and neuronal injury.¹ Modern assays detect anti-AQP4-IgG antibodies in approximately 80% of NMOSD patients.¹³ Serum anti-AQP4-IgG antibody titers have been shown to correlate with NMOSD clinical disease activity, drop after immunotherapy, and remain low during remissions.¹⁴ In addition, anti-AQP4-IgG antibody titers at the nadir of clinical attacks correlate with the length of longitudinally extensive spinal cord lesions.¹⁴

The prevalence of NMOSD is estimated at around 0.1 to 10 persons per 100,000 individuals, affecting approximately 15,000 individuals in the United States.¹¹ A 2019 to 2020 review of medical claims in the Oregon Medicaid population shows approximately 0.4 persons per 100,000 individuals have a diagnosis of NMOSD. NMOSD occurs in children and adults of all races, with a disproportionate prevalence among non-Caucasian females aged 30 to 40 years.¹¹ Danish and Caribbean-Africans appear to be at highest risk of being diagnosed with NMOSD.¹⁵ The reported incidence of NMOSD in women is up to 10 times higher than in men.¹⁶ It is difficult to determine exact prevalence rates as many NMOSD cases are never diagnosed and many others are misdiagnosed as MS.¹⁰ A positive assay for anti-AQP4-IgG antibodies is not required for a definitive diagnosis of NMOSD.⁸ Patients who test negative for anti-AQP4 antibodies, but meet clinical criteria for NMOSD, may have antibodies directed against other CNS proteins, and different lesion distributions.⁸ NMOSD in patients that are AQP4 seronegative is poorly understood. This subset of patients may comprise a heterogeneous population whose natural history and treatment response varies from NMOSD patients that are AQP4 seropositive.⁸

Patients with NMOSD may experience recurring relapses with accumulating disability which worsens with each relapse.¹⁷ From the first attack, many patients with NMOSD suffer permanent and severe disability, irrespective of age at onset.¹⁸ The risk of relapse is highest early in the course of the disease (~50 to 60% within the first year) and reported median time from onset attack to first relapse ranges from 8.5 to 14 months.¹⁹ The vast majority of patients (80 to 90%) experience repeated relapses, and disability accumulates with each relapse.¹⁷ Around 60% of patients relapse within 1 year of diagnosis and 90% relapse within 3 years.⁹ Individuals who experience relapses, on average, have higher annual direct medical costs and indirect societal costs than those without relapse over the first year following diagnosis.²⁰ The negative impact of NMOSD on patient quality of life (QoL) is predominantly a result of physical disability, pain, vision impairment, and bladder dysfunction.²¹ Disease-induced disability and symptoms have a considerable impact on patients' ability to work and thrive in social activities.²¹ Historically, the loss of motor and sensory function leads to approximately 50% of patients to require a wheelchair and 62% of patients become functionally blind, within 5 years of diagnosis.²²

The International Panel for NMO Diagnosis (IPND) was convened in 2011 to develop revised diagnostic criteria using systematic literature reviews and electronic surveys to facilitate consensus.¹³ The IPND consisted of 18 members from 9 countries and was led by 2 co-chairs.¹³ The panel agreed clinical diagnosis of NMOSD would be defined by integrating clinical, serologic, and neuroimaging data; diagnosis would not be based solely on detection of AQP4-IgG.¹³ Revised consensus criteria published in 2015, base the diagnosis of NMOSD on anti-AQP4-IgG antibody status, magnetic resonance imaging (MRI) neuroimaging features, and the presence of at least 1 or more specific clinical characteristics.¹³ The 6 core characteristics include:

- optic neuritis (eye pain, headache, blurred vision, color vision changes);
- acute myelitis (limb weakness or pain, spasticity of limbs or trunk, sensory disturbances);
- area postrema syndrome (unexplained hiccups or nausea and vomiting);
- acute brainstem syndrome (vomiting, hiccups, ocular movement disorders, pruritus, hearing loss, vertigo, facial palsy, trigeminal neuralgia) ;
- symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions;
- symptomatic cerebral syndrome with NMOSD-typical brain lesions.¹³

The panel concluded that criteria must define NMOSD in instances where AQP4-IgG serologic testing is negative or unavailable, especially because of the treatment implications.¹³ Diagnostic requirements are more stringent for patients in whom AQP4-IgG is not detected or for whom testing is unavailable.¹³ Such individuals must experience 2 or more different core clinical characteristics and other supportive MRI characteristics meant to enhance diagnostic specificity must also be present.¹³

The rationale for treatment of acute and recurrent attacks in NMOSD is based upon evidence that humoral autoimmunity plays a role in the pathogenesis of NMOSD, and is driven by the high attack-related disability, poor prognosis, and overall high risk of mortality in untreated patients.^{15,23} Acute attacks are treated with high dose IV methylprednisolone (1 gram daily for 3 to 5 days) and may be followed with an oral prednisone taper.¹⁵ Therapeutic plasmapheresis can be effective in patients with severe symptoms that fail to improve, or that progress despite treatment with corticosteroids.¹⁵ The key treatment goal is long-term disease stabilization via a reduction in relapse risk and preventing potential permanent disability.²⁴ Many clinicians use immunosuppressants including azathioprine, methotrexate, mycophenolate, cyclophosphamide, rituximab, mitoxantrone or tocilizumab off-label to prevent NMOSD relapses.²⁵ Only 4 comparative randomized trials of immunosuppressants have been published.²⁶⁻²⁹ Two trials were conducted in China,^{28,29} 1 trial was in Japan,²⁷ and the other was completed in Iran.²⁶ Limited observational evidence suggests that treatment of NMOSD with interferon beta,³⁰ natalizumab,³¹ or fingolimod³² is not effective and may be harmful. For patients with NMOSD who are seropositive for AQP4-IgG antibodies, treatment can be initiated with newer medications such as eculizumab, inebilizumab, or satralizumab. Characteristics of the 3 products recently FDA-approved for treatment of NMOSD patients who are AQP4-seropositive are presented in **Table 1**.

Table 1. FDA-Approved Treatments for Neuromyelitis Optica Spectrum Disorder

	Eculizumab (Soliris®)	Inebilizumab-cdon (Uplizna™)	Satralizumab-mwge (Enspryng™)
Administration Route	Intravenous	Intravenous	Subcutaneous
Recommended NMOSD dose	Loading Dose: 900 mg at weeks 0, 1, 2, 3 and 1200 mg at week 4 Maintenance Dose: 1200 mg every 2 weeks	Loading Dose: 300 mg at weeks 0, 2 Maintenance Dose: 300 mg every 6 months	Loading Dose: 120 mg at weeks 0, 2, 4 Maintenance Dose: 120 mg every 4 weeks
Primary Binding Target	Complement Protein C5	CD19 on B cells	IL-6 Receptor
Contraindications	Unresolved <i>Neisseria meningitidis</i> infection Not vaccinated against <i>Neisseria meningitidis</i>	Active Hepatitis B infection Active or Untreated Tuberculosis	Active Hepatitis B infection Active or Untreated Tuberculosis
Boxed Warning	Mandatory REMS program due to life-threatening and fatal meningococcal infections	None	None
Abbreviations: IL=interleukin; mg=milligram; NMOSD=Neuromyelitis Optica Spectrum Disorder; REMS = Risk Evaluation and Mitigation Strategies			

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

NEW DRUG EVALUATION: Eculizumab (Soliris®)

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Eculizumab (Soliris®) is a recombinant humanized monoclonal antibody that blocks the cleavage of the terminal complement protein C5 into C5a and C5b, which subsequently inhibits the formation of the membrane attack complex.¹ The membrane attack complex is implicated in astrocyte destruction and neuronal injury.¹ Eculizumab is FDA-approved for 4 indications: 1) reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH), 2) inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS), 3) treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive, and 4) treatment of NMOSD in adult patients who are anti-AQP4-IgG-antibody positive.³ The FDA-approval for the use of eculizumab to treat NMOSD was granted June 2019. Recommended eculizumab dosing for NMOSD consists of a 900 mg loading dose administered via intravenous (IV) infusion once weekly for the first 4 weeks, followed by 1200 mg 1 week later, then 1200 mg every 2 weeks thereafter.³ This summary will focus on evidence for use of eculizumab in treating NMOSD, and the other indications will be reviewed in the April 2021 class update of monoclonal C5 mediators.

A phase 3, double-blind, time-to-event, multicenter trial evaluated the safety and efficacy of eculizumab in adults with highly active AQP4-IgG seropositive NMOSD.¹ In the PREVENT trial, 143 patients were randomized 2:1 to receive either eculizumab or matched placebo. Patients required a history of 2 or more relapses in the 12 months prior to study enrollment or 3 relapses in the 24 months prior to enrollment and had an EDSS score of 7 or less.¹ Patients with an EDSS of 7 or less are unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair 12 hours a day.² Eculizumab was primarily add-on therapy: 78% of patients at baseline were receiving a stable-dose regimen of IST including chronic corticosteroids.¹ Eculizumab was initiated at a dose of 900 mg via IV infusion once weekly for 4 doses followed by 1200 mg every 2 weeks until first relapse, trial discontinuation, or the end of the trial.¹

The primary end point was the number of adjudicated initial relapses compared to placebo.¹ Secondary outcomes included the annualized relapse rate and the score on the Expanded Disability Status Scale (EDSS), which ranges from 0 (no disability) to 10 (death).¹ Relapse was defined as any new onset or worsening of previous neurologic symptoms with an objective change on neurologic examination that persisted for 24 hours or more, was attributable to NMOSD, and was not due to an alternate identifiable cause such as an infection, excessive exercise, or high ambient temperature.² The treating physician made the determination of whether the event met the protocol definition of a relapse.² The treating physician determined the appropriate acute treatment for the relapse, including whether to change any concurrent IST.² The severity of the relapse was determined using the assessments as conducted by the treating physician.² An amendment to the study protocol established a relapse adjudication process in which a Relapse Adjudication Committee (RAC), composed of three neurologists or neuro-ophthalmologists external to the applicant and blinded to treatment assignment, would review all investigator-reported relapse events and a decision regarding whether a relapse would be deemed an on-trial protocol-defined relapse would be rendered by the RAC in a majority vote.² The treatment arm was observed for a median duration of 90 weeks and the placebo arm was observed for a median duration of 43 weeks.¹ The study sponsor terminated the study prematurely at 23 adjudicated relapses because there had been no relapses in the prior two years, and it was deemed it unnecessary to await the 24th relapse.² Patients who completed the trial to a relapse or trial termination were eligible to enter an extension study of open-label eculizumab treatment.

Moderate quality evidence shows adjudicated relapses occurred in 3 of 96 patients (3%) in the eculizumab group and 20 of 47 (43%) in the placebo group (HR, 0.06; 95% CI, 0.02 to 0.20; P<0.001) over the follow-up period (median period: 90 weeks for active drug and 43 weeks for placebo).¹ A significant reduction in adjudicated annualized relapse rate was observed in patients treated with eculizumab compared with placebo (0.02 in the eculizumab group vs. 0.35 in the placebo group; RR, 0.045; 95% CI, 0.013 to 0.151; P<0.0001).¹ The mean change in the EDSS score (range 0 to 10) from baseline was not significantly different between the 2 treatment arms (-0.18 in the eculizumab group and 0.12 in the placebo group; LSMD, -0.29; 95% CI, -0.59 to 0.01).¹ The median change in EDSS was 0 for both treatment groups, and over 70% of eculizumab-treated patients had the same or experienced worsening of their EDSS scores at the end of study assessment.² Additional details of the PREVENT trial are described and evaluated below in **Table 4**.

Study Limitations:

The rationale for creating the RAC was to address an evident need for a more standardized approach to defining relapses due to “variability observed across sites in the diagnosis of relapse events.”² This committee was convened after 93 patients had been randomized and 23 relapses had occurred, relatively late in the study progression.² The RAC adjudicated confirmation rates of the previously investigator-determined relapses differed between events in the eculizumab and placebo treatment groups and suggested a possible bias.² Ultimately, the treating investigators in the PREVENT trial reported 43 distinct relapse events in placebo-treated patients and 36 unique relapse events in eculizumab patients.² However, in the eculizumab-treated patients, the RAC confirmed just 8% (3/36) of investigator-reported relapses as protocol-defined relapses whereas the RAC confirmation rate for placebo treatment patients was 49% (21/43).² The FDA reviewer noted the 3 confirmed events (2 optic neuritis attacks and 1 myelitis attack) in eculizumab-treated patients were appropriately adjudicated as relapses whereas the other 33 events were nonspecific neurological symptoms or transient phenomena that did not meet the protocol definition of a relapse.² The FDA reviewer also notes that the 21 adjudicated relapses in the placebo group met the protocol definition of a relapse, tended to be more extensive, and were associated with greater symptom severity than the 3 relapses in the eculizumab group.² Therefore, the FDA concluded that the RAC-adjudicated relapses were appropriate to serve as the basis of the primary efficacy analysis.² Analyses of several of the secondary measures that were included to provide clinical readouts of ambulatory function and quality of life were described nominally, but did not trend toward improvement. However, the study was not designed in a manner that allows for an accurate estimation of disability and quality of life outcomes.² The time-to-event design of the trial meant that there was not a uniform observation duration for all enrolled patients.²

Clinical Safety:

Eculizumab prescribing information contains a black box warning due to an increased risk of life-threatening and fatal meningococcal infections which was identified in initial trials evaluating eculizumab use in other indications.³ In clinical studies, 2 out of 196 PNH patients developed serious meningococcal infections while receiving treatment with eculizumab; both had been vaccinated.³ In clinical studies among non-PNH patients, meningococcal meningitis occurred in one unvaccinated patient.³ In addition, 3 out of 130 previously vaccinated patients with aHUS developed meningococcal infections while receiving treatment with eculizumab.³ All subjects enrolled in the PREVENT trial received immunization against meningococcal meningitis using regional vaccines.² No cases of meningococcal meningitis have been reported in adults with NMOSD.² Healthcare providers who prescribe eculizumab must enroll in the Solaris[®] Risk Evaluation and Mitigation Strategy (REMS) restricted program.³ Prescribers must counsel patients about the risk of meningococcal infection, provide patients with REM educational materials, and ensure patients are immunized with meningococcal vaccine at least 2 weeks prior to starting therapy.³ If urgent eculizumab therapy is warranted in an unvaccinated patient, the patient should begin a 2 week course of antibacterial drug prophylaxis.³ Vaccination reduces, but does not eliminate, the risk of meningococcal infections.³ Patients should be closely monitored for early signs and symptoms of meningococcal infection and evaluated immediately if an infection is suspected.³

The key risk of treatment with eculizumab is the risk of increased susceptibility to infections due to interference with the complement pathway.² Patients treated with eculizumab appeared to have a 1% higher risk of serious infections (most commonly, pneumonia) than placebo-treated patients.² This risk may be higher for infections with encapsulated organisms, most notably *Neisseria meningitidis*.² In the PREVENT trial, upper respiratory tract infections (29% vs. 13%), nasopharyngitis (21% vs. 19%), back pain (16% vs. 15%), and dizziness (15% vs. 13%) were more common in the eculizumab group compared with the placebo group.¹ There was one death from pulmonary empyema in the eculizumab group.¹ Infusion reactions were rare in the eculizumab group; only 2/96 (2%) patients experienced infusion reaction AEs that led to temporary study drug interruptions.² **Table 2** describes the adverse reactions experienced in 10% or greater of NMOSD patients treated with eculizumab.

Table 2. Adverse Reactions Reported in 10% or More of NMOSD patients treated with Eculizumab Compared with Placebo³

Adverse Events	Eculizumab (n=96)	Placebo (n=47)
Upper respiratory infection	29%	13%
Headache	23%	23%
Nasopharyngitis	21%	19%
Diarrhea	16%	15%
Dizziness	15%	13%
Back Pain	15%	13%
Arthralgia	11%	11%
Pharyngitis	10%	6%

Look-alike / Sound-alike Error Risk Potential: No issues identified

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Annualized relapse rate
- 2) Disability and functional status
- 3) Quality of life
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Reduction in risk of relapse

Table 3. Pharmacology and Pharmacokinetic Properties³

Parameter	
Mechanism of Action	Complement protein C5 inhibitor
Oral Bioavailability	N/A
Distribution and Protein Binding	Volume of distribution: 5 to 8 L; Protein Binding N/R
Elimination	N/R

		-Use of rituximab or mitoxantrone 3 mos prior to screening -Use of IVIG 3 weeks prior to screening -Use of prednisone > 20 mg/day -Unresolved meningococcal disease						<u>Comparator:</u> Placebo comparator as no other FDA-approved treatments were marketed at the time of the study. <u>Outcomes:</u> Relapse rates are clinically appropriate endpoints for NMOSD. <u>Setting:</u> 70 sites in 18 countries Americas: 31% Europe: 36% Asia-Pacific: 33%
<u>Abbreviations:</u> AQP4=Aquaporin-4; ARR=Absolute Risk Reduction; DB=double-blind; CI confidence interval; EDSS=Expanded Disability Status Scale; HR=Hazard Ratio; IST=immunosuppressive therapy; ITT=intention to treat; IV=intravenous; IVRS=Interactive Voice Response System; LSMD=Least Squares Mean Difference; MC=multi-center; mg=milligram; mos=months; N=number of subjects; NA=not applicable; NNH=number needed to harm; NNT=number needed to treat; NMO=Neuromyelitis Optica; NMOSD=Neuromyelitis Optic Spectrum Disorder; NS=Not Significant; PC=placebo-controlled; PG=parallel group; PP=per protocol; RCT=randomized clinical trial; yrs=years								

NEW DRUG EVALUATION: Inebilizumab-cdon (Uplizna™)

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Inebilizumab-cdon (Uplizna™), is a humanized monoclonal antibody indicated for the treatment of NMOSD in adult patients who are anti-AQP4 antibody positive.⁵ The antibody is afucosylated, which enhances antibody-dependent cellular cytotoxicity and improves therapeutic efficacy.³³ Inebilizumab is designed to bind the B cell-specific surface antigen CD19.³⁴ CD19 is expressed on a spectrum of B lymphocytes from pro-B cells to plasmablasts and is also present on some plasma cells.³⁴ B cells play an essential role in immune response to pathogens.³⁵ Binding of inebilizumab to CD19 results in depletion of B lymphocyte populations that express CD19.³⁴ Inebilizumab received FDA-approval in June 2020. Inebilizumab is also being studied for the treatment of myasthenia gravis, IgG4-related disease, and kidney transplant patients with high levels of alloantibodies. The recommended inebilizumab dosing is 300 mg via IV infusion followed 2 weeks later by a second 300 mg IV infusion followed by 300 mg IV infusion every 6 months (starting 6 months from the first infusion).⁵

N-MOMentum was a phase 2/3 double-blind trial that evaluated the safety and efficacy of inebilizumab as monotherapy in reducing the risk of relapse and disability in adults with AQP4 seropositive or seronegative NMOSD.⁴ Two hundred thirty participants were randomized 3:1 to inebilizumab or placebo at 99 clinical sites in 25 countries.⁴ Ninety-three percent (n=213) of enrolled subjects were AQP4 seropositive.⁴ Inebilizumab was administered as a 300 mg IV infusion dose on Days 1 and 15 of a 28-week randomized controlled period.⁴ All patients also received oral corticosteroids (prednisone 20 mg/day or equivalent) between Days 1 and 14, tapered to Day 21, to minimize the risk of an NMOSD attack immediately following the first inebilizumab treatment.⁴ No other use of immunosuppressants was permitted during the trial. The primary endpoint was to compare the efficacy of inebilizumab with placebo in reducing the risk of NMOSD attack in patients.⁴ An attack was defined as the presence of a new symptom(s) or worsening of an existing symptom(s) related to NMOSD that met the protocol-defined criteria for an attack upon neurological evaluation confirmed by an independent adjudication committee.⁴ Secondary endpoints included worsening of EDSS score compared to baseline (increase of ≥2 from baseline of 0, increase of ≥1 from baseline of 1–5, or increase of ≥ 0.5 from baseline of ≥ 5.5), change in low-contrast visual acuity binocular (LCVAB) score from baseline, total number of active MRI-lesions, and number of NMOSD-related hospitalizations.⁴ Lesion counts and hospitalizations were measured cumulatively up to the last visit of the randomized controlled period; disability worsening and visual acuity

were assessed at the last visit.⁴ An open-label phase is ongoing, with 213 participants receiving inebilizumab every 26 weeks (162 participants from the original inebilizumab group and 51 participants from the original placebo group).⁴

The randomized controlled period was stopped before complete enrollment, as recommended by the independent data-monitoring committee, because of a clear demonstration of inebilizumab efficacy.⁴ Moderate quality evidence showed 12% of (21/174) participants receiving inebilizumab in the intention-to-treat population had an attack versus 39% of (22/56) participants receiving placebo (HR, 0.272; 95% CI 0.150 to 0.496; $p < 0.0001$) before day 197 of the trial.⁴ Most attacks were myelitis and optic neuritis in both treatment groups.⁴ Fewer attacks in the inebilizumab group compared with the placebo group were graded as major (28.6% vs. 45.5%, respectively).⁴ In the AQP4 seropositive population, 11% (18/161) of patients receiving inebilizumab had an attack compared with 42% (22/52) of patients receiving placebo treatment (HR 0.227; 95% CI 0.121 to 0.423; $p < 0.0001$).⁴ Among the 17 AQP4-seronegative patients who were randomly allocated to treatment (13 to inebilizumab), three attacks occurred, all in the inebilizumab group.⁴ Because only four AQP4-seronegative patients were randomly allocated to placebo and no attack occurred in this group, inebilizumab efficacy could not be interpreted in the AQP4-seronegative cohort.⁴

Fewer patients had EDSS score worsening from baseline with inebilizumab than with placebo (15.5% vs 33.9%; odds ratio [OR]: 0.370 95% CI: 0.1850 to 0.7389; $p = 0.0049$).⁴ Cumulative new MRI lesion count was significantly lower in inebilizumab-treated patients compared with placebo-treated patients (1.6 vs 2.3 lesions in the subgroup with lesions; RR: 0.566 for total number of new lesions; 95% CI: 0.387 to 0.828; $p = 0.0034$).⁴ Cumulative number of NMOSD-related hospitalizations was lower for inebilizumab-treated patients compared with placebo-treated patients (mean: 1.0 vs 1.4 for the subgroup with hospitalizations; RR: 0.286; 95% CI: 0.111 to 0.741; $p = 0.010$).⁴ There was no significant change ($p = 0.97$) in low-contrast visual acuity from baseline as assessed by low-contrast Landolt C broken ring chart. Additional details of the N-Momentum trial are described and evaluated below in **Table 7**.

Study Limitations:

The study included only 17 AQP4 seronegative patients, representing 7% of the study population. Only four of these patients were in the placebo group, and they experienced no attacks.⁴ Therefore, the efficacy of inebilizumab in AQP4 seronegative patients could not be determined.⁴ Other study limitations include the variable observation periods between patients inherent in the time-to-event trial design (which also resulted in a significant amount of missing data), a consistent lack of relapse confirmation visits at an acceptable interval, and the protocol's inadequate approach to accounting for the impact of an acute relapse on EDSS changes from baseline.³⁴ The trial included a small study population and was of short duration (6 months). Post marketing trials are needed to assess long-term consequences of B-cell depletion (immunosuppression and opportunistic infections).³⁴ Although the trial was an international study that recruited patients from a wide range of backgrounds, inebilizumab has had little previous human exposure.³⁴ For safety reasons, patients with certain comorbidities or laboratory abnormalities were excluded.⁴ Direct head-to-head trials have not been conducted between inebilizumab and immunosuppressive or immunological treatments currently used in clinical practice for NMOSD.³⁴

Clinical Safety:

Across both the randomized and open-label treatment in the N-MOmentum trial, the most common adverse reactions (greater than or equal to 10%) were urinary tract infection (20%), nasopharyngitis (13%), infusion reaction (12%), arthralgia (11%), and headache (10%).⁵ Inebilizumab can cause infusion reactions, which can include headache, nausea, somnolence, dyspnea, fever, myalgia, rash, or other signs or symptoms.⁵ During the randomized clinical trial period, infusion reactions were observed with the first course of inebilizumab in 9% of AQP4 seropositive NMOSD patients and 10% of patients in the placebo arm.⁵ Infusion reactions were most common with the first infusion but were also observed during subsequent infusions.⁵ Premedication with IV methylprednisolone 80mg to 125 mg, oral diphenhydramine 25mg to 50mg and oral acetaminophen 500 mg to 650 mg is recommended prior to each infusion to reduce the frequency and severity of infusion reactions.⁵ Two deaths occurred in the inebilizumab cohort, but were not clearly attributable to active treatment.³⁴ Although

1 death was due to a brain lesion, it was not definitely proven to be due to progressive multifocal leukoencephalopathy (PML).³⁴ The drug label includes the presence of active infection as a contraindication to therapy and states that serious infections such as PML may occur during treatment with inebilizumab.³⁴ **Table 5** describes adverse reactions reported in 5% or greater of patients with AQP4 seropositive NMOSD compared to placebo.

Table 5. Adverse Reactions in Patients with NMOSD with an Incidence of Least 5% with Inebilizumab Compared with Placebo⁵

Adverse Reaction	Inebilizumab (N=161)	Placebo (n=52)
Urinary Tract Infection	11%	10%
Arthralgia	10%	4%
Headache	8%	8%
Back Pain	7%	4%

Look-alike / Sound-alike Error Risk Potential: No issues reported

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Annualized relapse rate
- 2) Disability status as evaluated by the EDSS
- 3) Functional status
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Reduction in risk of relapse

Table 6. Pharmacology and Pharmacokinetic Properties⁵

Parameter	
Mechanism of Action	CD19 B-cell binder
Oral Bioavailability	N/A
Distribution and Protein Binding	Volume of distribution: 2.95 L (central) and 2.57 L (peripheral); Protein Binding N/R
Elimination	Total body clearance: 0.19 L/day
Half-Life	18 days
Metabolism	Degraded by proteolytic enzymes throughout the body

Abbreviations: L=Liters; N/A=Not Applicable; NR=Not Reported

		- Active severe bacterial, viral, or other infection - History of hepatitis B and/or hepatitis C		1. 10 2. 8 RR 0.286 95%CI, 0.111 to 0.741 P=0.010	NA			
<p>Abbreviations: AQP4=Aquaporin-4; DB= double-blind; CI=confidence interval; EDSS=Expanded Disability Status Scale; HR=Hazard Ratio; IST=immunosuppressive therapy; ITT=intention to treat; IV=intravenous; IVIG= intravenous immunoglobulin; IVRS=Interactive Voice Response System; LCVAB=Low-Contrast Visual Acuity Binocular; LSMD=Least Squares Mean Difference; MC=multi-center; mg=milligram; mos=months; N=number of subjects; NA=not applicable; NNH=number needed to harm; NNT=number needed to treat; NMOSD=Neuromyelitis Optic Spectrum Disorder; NS=Not Significant; OR=odds ratio; PC=placebo-controlled; PP=per protocol; RR=rate ratio; RCT=randomized clinical trial; USA=United States of America; yo=years old; yrs=years</p>								

NEW DRUG EVALUATION: Satralizumab-mwge (Enspryng™)

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Satralizumab-mwge (Enspryng™) is a recombinant, humanized monoclonal antibody indicated for the treatment of NMOSD as monotherapy or in combination with IST in adult patients who are anti-AQP4 antibody positive.³⁶ Satralizumab prevents interleukin-6 (IL-6) from binding and inhibits IL-6 receptor signaling.⁶ IL-6 promotes the differentiation of naïve T cells into inflammatory T-helper-17 cells, which stimulate the differentiation of B cells into plasmablasts that produce AQP4-IgG.⁶ IL-6 increases the permeability of the blood–brain barrier, allowing penetration of AQP4-IgG and proinflammatory cells into the CNS.³⁷ Satralizumab received FDA breakthrough therapy designation in December 2018 for the treatment of NMOSD. Dosing begins with 120 mg subcutaneously (SC) self-administered every 2 weeks for the first 3 doses and then every 4 weeks thereafter.³⁶ The safety and efficacy of satralizumab in NMOSD patients were evaluated in two phase 3, randomized, placebo-controlled, multicenter, double-blinded studies with open-label extensions.^{6,7} In both studies, the primary endpoint was evaluated in the intent-to-treat (ITT) population, consisting of both AQP4 seropositive and AQP4 seronegative patients, and measured the time to first relapse.^{6,7} SAKuraSky⁶ investigated satralizumab added to baseline IST in adolescents and adults, while SAKuraStar⁷ evaluated satralizumab monotherapy in adults. Enrollment of AQP4 seronegative patients was limited to 30% in both trials to reflect estimated prevalence in the NMOSD population.

In the SAKuraSky trial, satralizumab was added to stable baseline azathioprine (AZA), mycophenolate mofetil (MMF), or glucocorticoids in adults aged 18 years and older.⁶ In adolescents aged 12 to 17 years (n=7), satralizumab was added to AZA or MMF in combination with glucocorticoids.⁶ No other baseline IST was permitted. Eighty-three patients were randomized 1:1 to satralizumab 120 mg SC or placebo, given at Weeks 0, 2, 4, and every four weeks thereafter, in addition to their baseline IST treatment.⁶ The primary end point was the first PDR in a time-to-event analysis.⁶ Relapses were defined via protocol as new or worsening objective neurological symptoms with at least one of the following:

- increase of 1.0 or more EDSS points from a baseline EDSS score of more than 0 (or increase of ≥ 2.0 EDSS points from a baseline EDSS score of 0);
- increase of 2.0 or more points on at least one appropriate symptom-specific functional system score;
- increase of 1.0 or more points on two or more symptom-specific functional system scores with a baseline of at least 1.0;
- or increase of 1.0 or more points on a single-eye symptom-specific functional system score with a baseline score of at least 1.0.⁶

Symptoms were required to be attributable to NMOSD, persisting for more than 24 hours, and not attributable to confounding clinical factors such as fever, infection, injury, change in mood, or adverse reactions to medications.⁶ Relapses were adjudicated by an independent Clinical Endpoint Committee (CEC) masked to treatment assignment. Key secondary end points were the change from baseline to week 24 in the visual-analogue scale (VAS) pain score (range, 0 to

100, with higher scores indicating more pain) and the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) score (range, 0 to 52, with lower scores indicating more fatigue).⁶ Evidence with other IL-6 antagonists has demonstrated reduction in pain and fatigue.⁶

Among patients who received satralizumab, 20% (n=8) experienced a PDR compared with 43% (n=18) of patients who received placebo (HR 0.38; 95% CI, 0.16 to 0.88; p=0.02) at 48 weeks.⁶ In AQP4-IgG seropositive patients, 11% of satralizumab-treated patients experienced a PDR at week 48 compared with 43% of placebo-treated patients (HR=0.66; 95% CI: 0.06-0.75; p=0.0086).⁶ There was no significant difference in relapse risk reduction for AQP4-IgG seronegative patients treated with satralizumab (n=14) versus placebo (n=14).⁶ The key secondary QoL outcome measures, change in baseline pain on the VAS and functional assessment of chronic fatigue on the FACIT-F scores, were not significantly different between treatment groups.⁶

In the SAKuraStar trial, satralizumab was evaluated as monotherapy in patients 18 to 74 years of age (N=95) at 44 sites in 13 countries.⁷ Eligible participants had experienced at least one documented NMOSD attack or relapse in the past 12 months and had a score of 6.5 or less on the EDSS.⁷ Exclusion criteria included clinical relapse 30 days or fewer before baseline.⁷ Patients were randomized 2:1 to satralizumab 120 mg SC or placebo, given at Weeks 0, 2, 4, and every four weeks thereafter.⁷ Taking immunosuppressants (i.e. AZA or MMF) concomitantly was prohibited.⁷ Corticosteroids and intravenous immunoglobulin were also prohibited except as rescue therapy; rescue therapy (e.g., pulse intravenous corticosteroids) was permitted for treatment of relapse.⁷ The primary endpoint was time to the first PDR, based on the intention-to-treat population and analyzed with stratification for two randomization factors (previous therapy for prevention of attacks and nature of the most recent attack).⁷ Protocol-defined relapses were similar to the parameters used in the SAKuraSky trial. Relapses were adjudicated by a Clinical Endpoint Committee (CEC) masked to treatment assignment. The double-blind phase was due to last until 44 protocol-defined relapses occurred or 1.5 years after random assignment of the last patient enrolled, whichever occurred first; participants could enter an open-label phase after the occurrence of a protocol-defined relapse or at the end of the double-blind phase.⁷ Key secondary end points were the change from baseline to week 24 in VAS pain score and the FACIT-F score. Additional predefined secondary outcomes were the proportion of relapse-free patients.⁷

Protocol-defined relapses occurred in 19 (30%) patients receiving satralizumab and 16 (50%) receiving placebo (HR 0.45, 95% CI 0.23 to 0.89; p=0.018).⁷ In AQP4-IgG seropositive patients, satralizumab showed a 74% reduction in the risk of relapse (HR=0.26; 95% CI: 0.11 to 0.63).⁷ The key secondary QoL outcome measures, change in baseline pain on the VAS and functional assessment of chronic fatigue on the FACIT-F scores, were not significantly different between treatment groups.⁷

Trial Limitations

Satralizumab reduced the risk of relapse in patients who were AQP4-IgG seropositive; however, there is insufficient evidence to indicate a risk reduction for the AQP4-IgG seronegative subgroup.⁷ The absence of observed efficacy in seronegative patients might be partly attributable to the greater degree of disease heterogeneity within the general AQP4-IgG seronegative subpopulation, as well as the small sample size.⁷ The study was not designed or powered to detect differences in efficacy within these subgroups.⁷ Findings from the SAKuraSky trial were not adequate to support any conclusions regarding satralizumab efficacy or safety in the adolescent population.⁷ Additional details of the 2 trials are described and evaluated below in **Table 11**.

Clinical Safety:

The most common risks of treatment with satralizumab were an increased risk of several types of infections (nasopharyngitis, upper respiratory tract infection) headache, rash, arthralgia, extremity pain, fatigue, and nausea. Other IL-6 antagonists (sarilumab and tocilizumab) have boxed warnings for serious infections and potential tuberculosis or hepatitis B reactivation.⁸ No cases of tuberculosis or hepatitis B were reported in satralizumab clinical trials because these patients were excluded. Injection site reactions occurred approximately 3% more often in satralizumab-treated patients compared with placebo.⁸ No deaths or

anaphylactic reactions were observed with satralizumab. Additional details regarding adverse events observed in the SAKuraStar and SAKuraSky trials are described in **Table 8** and **Table 9**, respectively.

Table 8. Adverse Reactions in Patients with NMOSD with an Incidence of Least 10% with Satralizumab Monotherapy Compared with Placebo³⁶

Adverse Reaction	Satralizumab (n=41)	Placebo (n=23)
Rash	17%	0%
Arthralgia	17%	0%
Pain in Extremity	15%	9%
Fatigue	15%	4%
Nausea	15%	9%
Nasopharyngitis	12%	4%
Pruritus	10%	0%
Depression	10%	0%
Cellulitis	10%	0%
Neutropenia	10%	4%
Increased blood phosphokinase	10%	4%
Fall	10%	4%

Table 9. Adverse Reactions in Patients with NMOSD with an Incidence of Least 10% with Satralizumab and IST Compared with Placebo and IST³⁶

Adverse Reaction	Satralizumab + IST (n=26)	Placebo + IST (n=26)
Nasopharyngitis	31%	15%
Headache	27%	12%
Upper respiratory tract infection	19%	12%
Gastritis	15%	0%
Arthralgia	12%	0%
Pharyngitis	12%	8%

Abbreviations: IST=Immunosuppressant Therapy

Look-alike / Sound-alike Error Risk Potential: None identified

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Annualized relapse rate
- 2) Reduction in pain as evaluated by VAS
- 3) Reduction in fatigue as evaluated by FACIT-F score
- 4) Functional status
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 2) Reduction in risk of relapse

Table 10. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	IL-6 antagonist
Subcutaneous Bioavailability	N/A
Distribution and Protein Binding	Volume of Distribution: 3.46 L (central) and 2.07 L (peripheral); Protein Binding N/R
Elimination	Clearance: 0.0601 L/day
Half-Life	30 days
Metabolism	Degraded by proteolytic enzymes throughout the body

Abbreviations: IL=interleukin; L=Liters; N/A=not applicable; N/R=Not Reported

<p>2. Trabousee A, et al.⁷</p> <p>SAkuraStar</p> <p>DB, PC, PG, MC, Phase 3 RCT</p>	<p>1. Satralizumab monotherapy 120 mg SC at weeks 0, 2, 4, and every 4 weeks thereafter</p> <p>2. Matched placebo administered SQ at week 0, 2, 4 and every 4 weeks thereafter</p> <p>Median Treatment Duration:</p> <p>1. 92 weeks (0-202 weeks)</p> <p>2. 55 weeks (2-216)</p> <p>Trial ended after 35 PDRs observed over 1.5 years</p>	<p>Demographics:</p> <p>-Anti-AQP4 antibody positive: 70%</p> <p>-Female: 81% female</p> <p>-Median age: 43 yr</p> <p>-Race:</p> <p>White: 65%</p> <p>Asian: 15%</p> <p>-Mean EDSS score: 3.8</p> <p>Key Inclusion Criteria:</p> <p>1. Adults aged 18 to 74 yrs with NMOSD</p> <p>2. AQP4 seropositive or seronegative</p> <p>3. At least 1 relapse in the 12 mos prior to screening</p> <p>4. EDSS score ≤ 6.5</p> <p>Key Exclusion Criteria:</p> <p>1. Concomitant IST therapy</p> <p>2. Relapse 30 days or less before study enrollment</p> <p>3. Any prior treatment with an IL-6 inhibitor, alemtuzumab, total lymphoid irradiation, or bone marrow transplant</p> <p>4. Anti-CD20 therapy, eculizumab, anti-B-lymphocyte stimulator monoclonal antibody, or any other MS disease-modifying treatment within 6 mos prior to screening</p> <p>5. Anti-CD4, cladribine, or mitoxantrone within 2 years</p>	<p>ITT:</p> <p>1. 63</p> <p>2. 32</p> <p>PP:</p> <p>1. 56</p> <p>2. 28</p> <p>Attrition:</p> <p>1. 7 (11%)</p> <p>2. 4 (13%)</p>	<p>Primary Endpoint: Number of patients with a protocol defined relapse in ITT population at week 48</p> <p>1.19 (30%)</p> <p>2.16 (50%)</p> <p>HR 0.45</p> <p>95% CI, 0.23 to 0.89</p> <p>P=0.018</p> <p>Secondary Endpoints:</p> <p>A. Percent of AQP4 seropositive subjects with protocol defined relapse</p> <p>1. 5 (11%) n=41</p> <p>2. 10 (43%) n=23</p> <p>HR 0.21</p> <p>95% CI 0.06 to 0.75</p> <p>p-value NR</p> <p>B. Change from baseline in VAS score for pain at 24 wks</p> <p>1. -2.74</p> <p>2. -5.95</p> <p>P=0.44</p> <p>C. Change in mean FACIT-F score from baseline to week 24 in ITT population</p> <p>1. 5.71</p> <p>2. 3.60</p> <p>P=NS</p> <p>D. Annualized Relapse Rate in ITT population</p> <p>1. 0.2</p> <p>2. 0.4</p> <p>Difference 0.2</p> <p>95% CI, 0.21 to 0.79</p> <p>p-value NR</p>	<p>20%/5</p> <p>32%/4</p> <p>NS</p> <p>NS</p> <p>NA</p>	<p>1. Adverse Events</p> <p>1. 58 (92%)</p> <p>2. 24 (75%)</p> <p>2. Serious Adverse Events</p> <p>1. 12 (19%)</p> <p>2. 5 (16%)</p> <p>3. Infections</p> <p>1. 34 (54%)</p> <p>2. 14 (44%)</p> <p>4. Injection-related Reactions</p> <p>1. 8 (13%)</p> <p>2. 3 (9%)</p> <p>95% CI and p-value NR for all</p>	<p>NA for all</p>	<p>Risk of Bias (low/high/unclear):</p> <p>Selection Bias: Unclear. Randomized 2:1 to satralizumab or placebo via IVRS. Subjects stratified by previous IST (B cell depletion vs. other IST) and nature of most recent symptoms (attack vs. relapse). Baseline demographics were balanced between treatment groups except for male gender (27% in treatment group vs. 3% in placebo group).</p> <p>Performance Bias: Low. Patients and all study personnel blinded to treatment assignment. Placebo matched in appearance to active drug.</p> <p>Detection Bias: Low. Relapse symptoms assessed separately from the treating investigator.</p> <p>Attrition Bias: Low. Attrition rates similar between treatment groups.</p> <p>Reporting Bias: Low. Protocol published online, all outcomes reported as outlined.</p> <p>Other Bias: High. Funded by Chugai Pharmaceutical (Roche). Employees of Roche participated in the design and conduct of the study, data collection, management, analysis, and interpretation.</p> <p>Applicability:</p> <p>Patient: Enrollment of AQP4 seropositive and seronegative subjects capped to reflect proportion of subjects in overall population.</p> <p>Intervention: Dosing used in study reflects effective dosing identified in Phase 2 trials.</p> <p>Comparator: Placebo selected as comparator as no other FDA-approved treatments were marketed at the time of the study.</p> <p>Outcomes: Relapse rates are clinically appropriate endpoints for NMOSD.</p> <p>Setting: 44 clinical sites in 13 countries: Bulgaria, Canada, Croatia, Georgia, Italy, Malaysia, Poland, Romania, South Korea, Taiwan, Turkey, United States, and Ukraine.</p>
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Abbreviations: AQP4=Aquaporin-4; ARR=Absolute Risk Reduction; AZA=azathioprine; DB= double-blind; CI=confidence interval; EDSS=Expanded Disability Status Scale; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; HR=Hazard Ratio; IST=immunosuppressive therapy; ITT=intention to treat; IV=intravenous; IVRS=Interactive Voice Response System; LCVAB=Low-Contrast Visual Acuity

Binocular; LSMD=Least Squares Mean Difference; MC=multi-center; mg=milligram; MMF = mycophenolate mofetil; mos=months; N=number of subjects; NA=not applicable; NNH=number needed to harm; NNT=number needed to treat; NMOSD=Neuromyelitis Optic Spectrum Disorder; NS=Not Significant; OCS=oral corticosteroid therapy; OR=odds ratio; PC=placebo-controlled; PG=parallel group; PP=per protocol; RR=rate ratio; RCT=randomized clinical trial; VAS= Visual Acuity Score; wks=weeks; yo=year old; yrs=years

References:

1. Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in Aquaporin-4–Positive Neuromyelitis Optica Spectrum Disorder. *N Engl J Med*. 2019;381(7):614-625.
2. Center for Drug Evaluation and Research. Eculizuamb Review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/125166Orig1s431.pdf Accessed January 13, 2021.
3. Soliris (eculizumab) Solution for Intravenous Infusion Prescribing Information. Boston, MA; Alexion Pharmaceuticals, Inc. 11/2020.
4. Cree BAC, Bennett JL, Kim HJ, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOMentum): a double-blind, randomised placebo-controlled phase 2/3 trial. *Lancet (London, England)*. 2019;394(10206):1352-1363.
5. Uplinza™(inebilizumab-cdon) Intravenous Injection Prescribing Information. Gaithersburg, MD; Viela Bio, Inc. 6/2020.
6. Yamamura T, Kleiter I, Fujihara K, et al. Trial of Satralizumab in Neuromyelitis Optica Spectrum Disorder. *N Engl J Med*. 2019;381(22):2114-2124.
7. Traboulsee A, Greenberg BM, Bennett JL, et al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. *The Lancet Neurology*. 2020;19(5):402-412.
8. Center for Drug Evaluation and Research. Satraliumab-mwge Review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/761149Orig1s000SumR.pdf Accessed January 15, 2021.
9. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. *The Lancet Neurology*. 2007;6(9):805-815.
10. Etemadifar M, Nasr Z, Khalili B, Taherioun M, Vosoughi R. Epidemiology of neuromyelitis optica in the world: a systematic review and meta-analysis. *Multiple sclerosis international*. 2015;2015:174720.
11. Flanagan EP, Cabre P, Weinshenker BG, et al. Epidemiology of aquaporin-4 autoimmunity and neuromyelitis optica spectrum. *Ann Neurol*. 2016;79(5):775-783.
12. Trebst C, Jarius S, Berthele A, et al. Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS). *J Neurol*. 2014;261(1):1-16.
13. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85(2):177-189.
14. Jarius S, Aboul-Enein F, Waters P, et al. Antibody to aquaporin-4 in the long-term course of neuromyelitis optica. *Brain*. 2008;131(Pt 11):3072-3080.
15. Sellner J, Boggild M, Clanet M, et al. EFNS guidelines on diagnosis and management of neuromyelitis optica. *Eur J Neurol*. 2010;17(8):1019-1032.
16. Wingerchuk DM. Neuromyelitis optica: effect of gender. *J Neurol Sci*. 2009;286(1-2):18-23.
17. Wingerchuk DM. Diagnosis and treatment of neuromyelitis optica. *Neurologist*. 2007;13(1):2-11.

18. Palace J, Lin DY, Zeng D, et al. Outcome prediction models in AQP4-IgG positive neuromyelitis optica spectrum disorders. *Brain*. 2019;142(5):1310-1323.
19. Sherman E, Han MH. Acute and Chronic Management of Neuromyelitis Optica Spectrum Disorder. *Current treatment options in neurology*. 2015;17(11):48.
20. Stafkey-Mailey D, Boscoe A, Ajmera M, Mauskopf J, Iloeje U, Levy M. A Real-World Analysis of Relapses and Costs of Neuromyelitis Optica Spectrum Disorders Using a United States Administrative Claims Database (P6.161). *Neurology*. 2016;86(16 Supplement):P6.161.
21. Beekman J, Keisler A, Pedraza O, et al. Neuromyelitis optica spectrum disorder: Patient experience and quality of life. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(4):e580.
22. Kessler RA, Mealy MA, Levy M. Treatment of Neuromyelitis Optica Spectrum Disorder: Acute, Preventive, and Symptomatic. *Current treatment options in neurology*. 2016;18(1):2.
23. Collongues N, de Seze J. Current and future treatment approaches for neuromyelitis optica. *Therapeutic advances in neurological disorders*. 2011;4(2):111-121.
24. Kimbrough DJ, Fujihara K, Jacob A, et al. Treatment of Neuromyelitis Optica: Review and Recommendations. *Mult Scler Relat Disord*. 2012;1(4):180-187.
25. Fujihara K. Neuromyelitis optica spectrum disorders: still evolving and broadening. *Current opinion in neurology*. 2019;32(3):385-394.
26. Nikoo Z, Badihian S, Shaygannejad V, Asgari N, Ashtari F. Comparison of the efficacy of azathioprine and rituximab in neuromyelitis optica spectrum disorder: a randomized clinical trial. *J Neurol*. 2017;264(9):2003-2009.
27. Tahara M, Oeda T, Okada K, et al. Safety and efficacy of rituximab in neuromyelitis optica spectrum disorders (RIN-1 study): a multicentre, randomised, double-blind, placebo-controlled trial. *The Lancet Neurology*. 2020;19(4):298-306.
28. Yang Y, Wang CJ, Wang BJ, Zeng ZL, Guo SG. Comparison of efficacy and tolerability of azathioprine, mycophenolate mofetil, and lower dosages of rituximab among patients with neuromyelitis optica spectrum disorder. *J Neurol Sci*. 2018;385:192-197.
29. Zhang C, Zhang M, Qiu W, et al. Safety and efficacy of tocilizumab versus azathioprine in highly relapsing neuromyelitis optica spectrum disorder (TANGO): an open-label, multicentre, randomised, phase 2 trial. *The Lancet Neurology*. 2020;19(5):391-401.
30. Shimizu J, Hatanaka Y, Hasegawa M, et al. IFN β -1b may severely exacerbate Japanese optic-spinal MS in neuromyelitis optica spectrum. *Neurology*. 2010;75(16):1423-1427.
31. Barnett MH, Prineas JW, Buckland ME, Parratt JD, Pollard JD. Massive astrocyte destruction in neuromyelitis optica despite natalizumab therapy. *Multiple sclerosis (Houndmills, Basingstoke, England)*. 2012;18(1):108-112.
32. Min JH, Kim BJ, Lee KH. Development of extensive brain lesions following fingolimod (FTY720) treatment in a patient with neuromyelitis optica spectrum disorder. *Multiple sclerosis (Houndmills, Basingstoke, England)*. 2012;18(1):113-115.
33. Pereira NA, Chan KF, Lin PC, Song Z. The "less-is-more" in therapeutic antibodies: Afucosylated anti-cancer antibodies with enhanced antibody-dependent cellular cytotoxicity. *mAbs*. 2018;10(5):693-711.
34. Center for Drug Evaluation and Research. Inebilizumab Review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/761142Orig1s000PharmR.pdf. Accessed January 14.
35. Cree BA, Bennett JL, Sheehan M, et al. Placebo-controlled study in neuromyelitis optica-Ethical and design considerations. 2016;1(7):862-872.
36. EnspryTM (satralizumab) Subcutaneous Injection Prescribing Information. South San Francisco, CA; Genentech USA, Inc. August 2020.

37. Takeshita Y, Obermeier B, Cotleur AC, et al. Effects of neuromyelitis optica–IgG at the blood–brain barrier in vitro. *Neurology - Neuroimmunology Neuroinflammation*. 2017;4(1):e311.

Appendix 1: Current Preferred Drug List

Class	Generic	Brand	Route	Form	PDL
Biologics for Rare Diseases	eculizumab	SOLIRIS	IV	VIAL	
Biologics for Rare Diseases	inebilizumab-cdon	UPLIZNA	IV	VIAL	
Biologics for Rare Diseases	satralizumab-mwge	ENSPRYNG	SUB-Q	SYRINGE	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to January Week 2, 2021, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 15, 2021

- | | | |
|----|----------------------------------|------|
| 1. | <i>exp Neuromyelitis Optica/</i> | 2806 |
| 2. | <i>inebilizumab.mp.</i> | 29 |
| 3. | <i>eculizumab.mp.</i> | 1792 |
| 4. | <i>satralizumab.mp</i> | 20 |
| 5. | <i>2 or 3 or 4</i> | 1812 |
| 6. | <i>1 and 5</i> | 26 |

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SOLIRIS safely and effectively. See full prescribing information for SOLIRIS.

SOLIRIS® (eculizumab) injection, for intravenous use
Initial U.S. Approval: 2007

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS See full prescribing information for complete boxed warning

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris and may become rapidly life-threatening or fatal if not recognized and treated early (5.1).

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies (5.1).
- Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risks of developing a meningococcal infection. (See *Warnings and Precautions* (5.1) for additional guidance on the management of the risk of meningococcal infection.)
- Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

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 (5.1).

RECENT MAJOR CHANGES

Indications and Usage (1.4)	06/2019
Dosage and Administration (2.4, 2.5)	06/2019
Dosage and Administration (2.5, 2.6, 2.7)	07/2018
Warnings and Precautions (5.1, 5.2)	07/2018

INDICATIONS AND USAGE

Soliris is a complement inhibitor indicated for:

- The treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis (1.1).
- The treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (1.2).

Limitation of Use

Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

- The treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive (1.3).

- The treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive (1.4).

DOSAGE AND ADMINISTRATION

For intravenous infusion only
PNH Dosage Regimen: (2.2)
aHUS Dosage Regimen: (2.3)
gMG and NMOSD Dosage Regimen: (2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 300 mg/30 mL (10 mg/mL) in a single-dose vial (3).

CONTRAINDICATIONS

Soliris is contraindicated in:

- Patients with unresolved serious *Neisseria meningitidis* infection (4).
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection (5.1).

WARNINGS AND PRECAUTIONS

- Discontinue Soliris in patients who are being treated for serious meningococcal infections (5.1).
- Use caution when administering Soliris to patients with any other systemic infection (5.2).

ADVERSE REACTIONS

The most frequently reported adverse reactions in the PNH randomized trial ($\geq 10\%$ overall and greater than placebo) are: headache, nasopharyngitis, back pain, and nausea (6.1).

The most frequently reported adverse reactions in aHUS single arm prospective trials ($\geq 20\%$) are: headache, diarrhea, hypertension, upper respiratory infection, abdominal pain, vomiting, nasopharyngitis, anemia, cough, peripheral edema, nausea, urinary tract infections, pyrexia (6.1).

The most frequently reported adverse reaction in the gMG placebo-controlled clinical trial ($\geq 10\%$) is: musculoskeletal pain (6.1).

The most frequently reported adverse reactions in the NMOSD placebo-controlled trial ($\geq 10\%$) are: upper respiratory infection, nasopharyngitis, diarrhea, back pain, dizziness, influenza, arthralgia, pharyngitis, and contusion (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2019

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use UPLIZNA™ safely and effectively. See full prescribing information for UPLIZNA™.

UPLIZNA™ (inebilizumab-cdon) injection, for intravenous use
Initial U.S. Approval: 2020

INDICATIONS AND USAGE

UPLIZNA is a CD19-directed cytolytic antibody indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive. (1)

DOSAGE AND ADMINISTRATION

- Hepatitis B virus, quantitative serum immunoglobulins, and tuberculosis screening is required before the first dose (2.1)
- Prior to every infusion:
 - Determine if there is an active infection (2.2, 5.2)
 - Premedicate with a corticosteroid, an antihistamine, and an antipyretic (2.2, 5.1)
- UPLIZNA must be diluted in 250 mL of 0.9% Sodium Chloride Injection, USP prior to administration (2.3, 2.4)
- UPLIZNA is administered as an intravenous infusion titrated to completion, approximately 90 minutes. The recommended dose is:
 - Initial dose: 300 mg intravenous infusion followed two weeks later by a second 300 mg intravenous infusion
 - Subsequent doses (starting 6 months from the first infusion): single 300 mg intravenous infusion every 6 months (2.3)
- Monitor patients closely during the infusion and for at least one hour after completion of the infusion (2.3)

DOSAGE FORMS AND STRENGTHS

- Injection: 100 mg/10 mL (10 mg/mL) solution in a single-dose vial (3)

CONTRAINDICATIONS

- Previous life-threatening reaction to infusion of UPLIZNA (4)
- Active hepatitis B infection (4)
- Active or untreated latent tuberculosis (4)

WARNINGS AND PRECAUTIONS

- Infusion reactions: Administer premedications prior to infusion (2.2). Management recommendations for infusion reactions depend on the type and severity of the reaction. Permanently discontinue UPLIZNA if a life-threatening or disabling infusion reaction occurs (5.1)
- Infections: Delay UPLIZNA administration in patients with an active infection until the infection is resolved. Vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation, until B-cell repletion (5.2)
- Immunoglobulin levels: Monitor the level of immunoglobulins at the beginning, during, and after discontinuation of treatment with UPLIZNA until B-cell repletion. Consider discontinuing UPLIZNA if a patient develops a serious opportunistic infection or recurrent infections if immunoglobulin levels indicate immune compromise (5.3)
- Fetal Risk: May cause fetal harm based on animal data. Advise females of reproductive potential of the potential risk to a fetus and to use an effective method of contraception during treatment and for 6 months after stopping UPLIZNA (5.4, 8.1)

ADVERSE REACTIONS

The most common adverse reactions (at least 10% of patients treated with UPLIZNA and greater than placebo) were urinary tract infection and arthralgia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact **Viela Bio, Inc.** at 1-855-558-4352 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 6/2020

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENSPRYNG safely and effectively. See full prescribing information for ENSPRYNG.

ENSPRYNG™ (satralizumab-mwge) injection, for subcutaneous use
Initial U.S. Approval: 2020

INDICATIONS AND USAGE

ENSPRYNG is an interleukin-6 (IL-6) receptor antagonist indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive. (1)

DOSAGE AND ADMINISTRATION

- Hepatitis B virus, tuberculosis, and liver transaminase screening is required before the first dose. (2.1)
- Prior to every use, determine if there is an active infection. (2.2)
- The recommended loading dosage of ENSPRYNG for the first three administrations is 120 mg by subcutaneous injection at Weeks 0, 2, and 4, followed by a maintenance dosage of 120 mg every 4 weeks. (2.2)
- See Full Prescribing Information for important preparation and administration instructions. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/mL in a single-dose prefilled syringe (3)

CONTRAINDICATIONS

- Known hypersensitivity to satralizumab or any of the inactive ingredients (4)
- Active Hepatitis B infection (4)
- Active or untreated latent tuberculosis (4)

WARNINGS AND PRECAUTIONS

- Infections: Delay ENSPRYNG administration in patients with an active infection until the infection is resolved. Vaccination with live or live-attenuated vaccines is not recommended during treatment. (5.1)
- Elevated Liver Enzymes: Monitor ALT and AST levels during treatment; interruption of ENSPRYNG may be required. (5.2)
- Decreased Neutrophil Counts: Monitor neutrophils during treatment. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (incidence at least 15%) are nasopharyngitis, headache, upper respiratory tract infection, gastritis, rash, arthralgia, extremity pain, fatigue, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2020

Eculizumab (Soliris®)

Goal(s):

- Restrict use to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Eculizumab is FDA-approved for:
 - Neuromyelitis Optica Spectrum Disorder (NMOSD) in adult patients who are anti-AQP4-IgG-antibody positive
 - Reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH)
 - Inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS)
 - Treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor (AChR) antibody positive

Length of Authorization:

Up to 12 months

Requires PA:

- Soliris® (eculizumab) physician administered claims

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	Yes: Go to #3	No: Pass to RPh. Deny; not funded by the OHP.
3. Is this request for continuation of therapy?	Yes: Go to Renewal Criteria	No: Go to #4

Approval Criteria		
4. Has the patient been vaccinated against <i>Neisseria meningitides</i> according to current Advisory Committee on Immunization Practice (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness
5. Is the diagnosis one of the following: <ul style="list-style-type: none"> • Neuromyelitis Optica Spectrum Disorder (NMOSD) in an adult who is anti-aquaporin-4 (AQP4) antibody positive, • Paroxysmal Nocturnal Hemoglobinuria (PNH), <p style="text-align: center; margin: 10px 0;">OR</p> <ul style="list-style-type: none"> • atypical Hemolytic Uremic Syndrome (aHUS)? (Note: Eculizumab is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS). 	Yes: Go to #6	No: Go to #7
6. Does the requested dosing align with the FDA- approved dosing (Table 1)?	Yes: Approve for 12 months	No: Pass to RPh. Deny; medical appropriateness
7. Is the request for a diagnosis of myasthenia gravis (MG) ACh Receptor (AChR) antibody-positive?	Yes: Go to #8	No: Pass to RPh. Deny; medical appropriateness

Approval Criteria		
<p>8. Has the patient tried:</p> <ul style="list-style-type: none"> at least 2 or more immunosuppressant therapies (e.g., glucocorticoids in combination with azathioprine or mycophenolate mofetil or cyclosporine or tacrolimus or methotrexate or rituximab) for 12 months without symptom control OR at least 1 or more nonsteroidal immunosuppressant with maintenance intravenous immunoglobulin once monthly or plasma exchange therapy (PLEX) over 12 months without symptom control? 	Yes: Go to #9	No: Pass to RPh. Deny; medical appropriateness
<p>9. Is the Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score ≥ 6?</p>	Yes: Approve for 12 months	No: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
<p>1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom control or improvement, functional improvement, etc.).</p>	<p>Yes: Approve for 12 months</p> <p>Document baseline assessment and physician attestation received.</p>	No: Pass to RPh. Deny; medical appropriateness

Table 1. FDA-Approved Indications and Dosing for Eculizumab¹

	Eculizumab (Soliris®)
FDA-approved Indications	<ul style="list-style-type: none"> Neuromyelitis Optica Spectrum Disorder (NMOSD) in adult patients who are anti-AQP4-IgG-antibody Reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH) Inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS) Treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive

Recommended NMOSD dose in patients 18 yo and older	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter		
Recommended PNH dose in patients 18 yo and older	600 mg IV every week x 4 weeks, followed by 900 mg IV for the fifth dose 1 week later, then 900 mg IV every 2 weeks thereafter		
Recommended aHUS dose in patients less than 18 yo	Body Weight	Induction Dose	Maintenance Dose
	5 kg to 9 kg	300 mg weekly x 1 dose	300 mg at week 2; then 300mg every 3 weeks
	10 kg to 19 kg	600 mg weekly x 1 dose	300 mg at week 2; then 300mg every 2 weeks
	20 kg to 29 kg	600 mg weekly x 2 doses	600 mg at week 3; then 600mg every 2 weeks
	30 kg to 39 kg	600 mg weekly x 2 doses	900 mg at week 3; then 900 mg every 2 weeks
	≥ 40 kg	900 mg weekly x 4 doses	1200 mg at week 5; then 1200 mg every 2 weeks
Recommended aHUS dose in patients 18 yo and older	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter		
Recommended generalized MG dose	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter		
Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion	Dependent on most recent eculizumab dose: refer to prescribing information for appropriate dosing (300 mg to 600 mg)		

1. Soliris (eculizumab) Solution for Intravenous Infusion Prescribing Information. Boston, MA: Alexion Pharmaceuticals, Inc. 11/2020.

P&T/DUR Review: 4/21 (DM)
Implementation: TBD

Inebilizumab-cdon (Uplizna™)

Goal(s):

- Restrict use to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.

Length of Authorization:

Up to 12 months

Requires PA:

- Uplizna™ (Inebilizumab-cdon) physician administered claims

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	Yes: Go to #6	No: Pass to RPh. Deny; not funded by the OHP.
3. Is this request for continuation of therapy?	Yes: Go to Renewal Criteria	No: Go to # 4
4. Is the request for Neuromyelitis Optica Spectrum Disorder (NMOSD) in an adult who is anti-aquaporin-4 (AQP4) antibody positive?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness
5. Has the patient been screened for Hepatitis B and tuberculosis infection?	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness
6. Does the patient have active Hepatitis B or untreated latent tuberculosis?	Yes: Pass to RPh. Deny; medical appropriateness	No: Approve for 12 months
Renewal Criteria		

Approval Criteria

1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom improvement, functional improvement, etc.).

Yes: Approve for 12 months

Document baseline assessment and physician attestation received.

No: Pass to RPh. Deny; medical appropriateness

*P&T/DUR Review: 4/21 (DM)
Implementation: TBD*

Satralizumab-mwge (Enspryng™)

Goal(s):

- Restrict use to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.

Length of Authorization:

Up to 12 months

Requires PA:

- Enspryng™ (Satralizumab-mwge) pharmacy claims

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	Yes: Go to #3	No: Pass to RPh. Deny; not funded by the OHP.
3. Is this request for continuation of therapy?	Yes: Go to Renewal Criteria	No: Go to # 4
4. Is the request for Neuromyelitis Optica Spectrum Disorder (NMOSD) in an adult who is anti-aquaporin-4 (AQP4) antibody positive?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness
5. Has the patient been screened for Hepatitis B and tuberculosis infection?	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness
6. Does the patient have active Hepatitis B or untreated latent tuberculosis?	Yes: Pass to RPh. Deny; medical appropriateness	No: Approve for 12 months
Renewal Criteria		
1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom improvement, functional improvement, etc.).	Yes: Approve for 12 months Document baseline assessment and physician attestation received.	No: Pass to RPh. Deny; medical appropriateness