CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761149Orig1s000

SUMMARY REVIEW

Summary Review

Date	August 14, 2020
From	Paul R Lee MD, PhD, Acting Deputy Director, Division of Neurology 2 (DN2) Nick Kozauer, MD, Acting Director, DN2 Billy Dunn, MD, Director, Office of Neuroscience
Subject	Summary Review
BLA #	761149
Applicant	Roche/Genentech
Date of Submission	August 15, 2019
PDUFA Goal Date	August 15, 2020
Proprietary Name	Enspryng
Established or Proper Name	Satralizumab-mwge
Dosage Form(s)	120 mg/mL in a single-dose prefilled syringe via subcutaneous injection
Applicant Proposed Indication(s)/Population(s)	Adults with neuromyelitis optica spectrum disorders (NMOSD)
Applicant Proposed Dosing Regimen(s)	120 mg at Weeks 0, 2 and 4, and every 4 weeks thereafter
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	The treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive
Recommended Dosing Regimen(s) (if applicable)	Same as proposed

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Neuromyelitis optica spectrum disorder (NMOSD), formerly known as "NMO" or "Devic's Disease," is an autoimmune disease that is characterized by clinical "attacks" or relapses in which patients experience inflammation of the optic nerve (optic neuritis), spinal cord (transverse myelitis), or brainstem. These inflammatory episodes can cause blindness, paralysis, loss of sensation, bowel or bladder dysfunction, and other serious, disabling symptoms. The diagnosis of NMOSD relies on a clinician's assessment of a patient's history and findings being consistent with consensus international clinical criteria for NMOSD. Almost all patients with NMOSD have more than one relapse. Few patients who experience an NMOSD relapse have a full recovery. More than half of patients with NMOSD have permanent blindness or paralysis as the result of NMOSD relapses. If inflammation compromises brainstem regions involved in breathing or heart function, which occurs rarely, NMOSD relapses can be fatal.

Most patients diagnosed with NMOSD are women. The average age of patients with NMOSD is over 40 years old, though onset can occur throughout the lifespan. Onset in childhood occurs very rarely and the pediatric manifestation of NMOSD is poorly understood. The epidemiology of NMOSD is complex and differs greatly depending on the region and the ethnicity of the study population. The incidence of NMOSD is estimated between 0.05-0.4 per 100,000 population, and the prevalence estimates vary from 0.5-10 per 100,000 population. African and Danish subpopulations appear to be at highest risk of developing NMOSD. Most NMOSD cases are sporadic, but NMOSD cases can cluster in families who have human leukocyte antigen genotypes conferring a genetic susceptibility to autoimmunity.

The pathophysiology of NMOSD is not fully elucidated, but many patients with NMOSD have antibodies directed against the aquaporin-4 (AQP4) protein which form membrane bound water transporters in cells throughout the central nervous system (CNS). AQP4 is highly expressed in the optic nerves, spinal cord, and area postrema of the brainstem, and it is these regions of the CNS that are often targeted for inflammation in NMOSD relapses. However, there are patients who do not have antibodies directed against AQP4 who experience NMOSD relapses and appear similar to patients who are anti-AQP4 antibody positive. Therefore, the current NMOSD diagnostic criteria in widespread use rely on the presence of cardinal clinical features such as optic neuritis and longitudinally extensive transverse myelitis. A positive assay for anti-AQP4 antibodies is not required for definitive diagnosis of NMOSD. Patients who test negative for anti-AQP4 antibodies, but meet clinical

criteria for NMOSD, may have antibodies directed against other CNS proteins, different lesion distributions, and may experience a monophasic clinical course. NMOSD in patients testing negative for anti-AQP4 antibodies is poorly understood and this subset of NMOSD patients may comprise a heterogeneous population whose natural history and treatment response differs from those of patients with anti-AQP4 antibodies.

Enspryng (satralizumab-mwge) is a humanized IgG2 monoclonal antibody that binds to the interleukin-6 (IL-6) receptor. When satralizumab-mwge binds to IL-6 receptor on a cell's surface, it prevents binding of IL-6 and therefore inhibits IL-6 signaling through the IL-6 receptor. Though the exact mechanism of action of satralizumab-mwge is unknown, by inhibiting IL-6 signaling, satralizumab-mwge is intended to interfere with the IL-6 component of the immune response and thereby lower the likelihood of relapses associated with the pathological autoimmune processes related to IL-6 that are presumed to occur in NMOSD. Sarilumab and tocilizumab, which are also monoclonal antibodies targeting the IL-6 receptor, are approved, effective therapies for the treatment of autoimmune diseases such as rheumatoid arthritis, giant cell arteritis, and juvenile idiopathic arthritides.

The applicant provides data from two studies, Studies 307JG (also known as bn40898) and 309JG (also known as bn40900), which were both prospective, double-blind, placebo-controlled, randomized trials. These two trials evaluated a 120 mg dose of satralizumab-mwge (or placebo) given subcutaneously once on the first day of treatment, followed by a second dose two weeks later, a third dose four weeks after the initial treatment, followed by single 120 mg doses every month thereafter. Enrollment in either trial required that patients met the 2006 international criteria for NMO; these patients would qualify for a diagnosis of NMOSD using the current international diagnostic criteria. The primary outcome efficacy measure of these trials was the time from Day 1 of trial randomization to the onset of a protocol defined, confirmed relapse or to the end of the randomized controlled phase of the trial. All reported relapses were subject to review by an independent confirmation committee (the Clinical Events Committee or CEC), and only CEC-confirmed relapses were considered in the statistical analysis of the primary endpoint.

Study 307JG randomized 83 patients in a 1:1 ratio to treatment with satralizumab-mwge or placebo. Patients enrolled in Study 307JG could remain on baseline treatment with azathioprine, mycophenolate mofetil, or oral corticosteroids at a stable dose; no other baseline immunosuppressant treatments were permitted. The majority (66%) of the patients enrolled in this clinical trial were anti-AQP4 antibody positive. There were 41 patients with NMOSD (27 of whom were anti-AQP4 antibody positive) randomized to satralizumab-mwge treatment and 42 patients (28 of whom were anti-AQP4 antibody positive) randomized to placebo treatment. There were 28 patients who were negative for anti-AQP4 antibodies. Seven patients enrolled in this trial were less than 18 years old, 3 of these patients were anti-AQP4 antibody positive (2 were randomized to treatment with satralizumab-mwge, one to placebo.)

Study 309JG randomized 95 adult patients in a 2:1 ratio to treatment with satralizumab-mwge or placebo. Unlike Study 307JG, patients could not continue treatment on any concurrent immunosuppressant therapies in this trial. Over half (56%) of the patients enrolled in this trial were anti-AQP4 antibody positive. There were 63 patients with NMOSD (31 of whom were anti-AQP4 antibody positive) randomized to satralizumab-mwge treatment and 32 patients (22 of whom were anti-AQP4 antibody positive) randomized to placebo treatment. There were 42 patients who were negative for anti-AQP4 antibodies.

In both Studies 307JG and 309JG, patients with NMOSD who were positive for anti-AQP4 antibodies in the satralizumab-mwge treatment arm experienced a statistically significant (p=0.0086 and 0.0014, respectively) 76-79% reduction in relapse risk during the trials, compared to placebo. There was no effect of treatment on relapses in either study for patients with NMOSD who were negative for anti-AQP4 antibodies. Findings in a pediatric patient subgroup of seven patients in Study 307JG were not adequate to support any conclusions regarding efficacy or safety in patients less than 18 years old. The key secondary outcome measures, change from baseline in the visual analog scale (VAS) and functional assessment of chronic illness therapy (FACIT) scores, were not significantly different between treatment groups in either study.

The safety findings in Studies 307JG and 309JG showed that satralizumab-mwge was generally well-tolerated. The adverse events associated with satralizumab-mwge included expected risks associated with immune suppression using an anti-IL-6 receptor antagonist such as a potential greater risk of infections, including serious infections, although few serious infections were observed, likely because of the small sample size. There were no deaths reported in patients treated with satralizumab-mwge. The most common treatment-emergent adverse events aside from mild infections were rash, headache, and pain in joints or extremities. A required postmarketing pregnancy observation trial will examine outcomes from fetal exposure because animal data suggest satralizumab-mwge exposure may alter the immune system of offspring. No safety issues were identified that would require a risk evaluation and mitigation strategy (REMS).

Two adequate and well-controlled studies (Studies 307JG and 309JG) provided substantial evidence that satralizumab-mwge is an effective treatment of NMOSD in adult patients who are anti-AQP4 antibody positive. These studies' findings did not support a conclusion that satralizumab-mwge is an effective treatment for patients with NMOSD who were anti-AQP4 antibody negative. The most common potentially serious safety risk of satralizumab-mwge, increased risk of serious infections, can be addressed through labeling and does not preclude approval of this effective therapy.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• NMOSD is an autoimmune condition that is associated with relapses that predominantly involve inflammation in the spinal cord and optic nerves. The global prevalence of NMOSD is between 0.5 and 10 per 100,000 population. The female-to-male ratio is approximately 5:1. There may be as many as 12,000 patients with NMOSD in the United States. Individuals of Danish and Caribbean-African descent appear to be at highest risk of being diagnosed with NMOSD.	NMOSD is a rare, serious, neuroinflammatory disease that is diagnosed predominantly in women.
	• NMOSD relapses can result in severe and largely irreversible neurologic disability, including blindness, paralysis, and death due to respiratory failure. The spectrum of the severity of relapses in patients with NMOSD is uncertain. Although some relapses may be very severe, other relapses may result in mild or moderate disability. Full recovery from NMOSD relapses is rare.	Relapses in patients with NMOSD can cause serious, lifelong disability and can even be fatal. Preventing and reducing the frequency of relapses is a meaningful clinical outcome for patients with NMOSD.
	• Current international consensus diagnostic criteria define NMOSD based on the presence of core features of NMOSD such as optic neuritis, acute myelitis, and brainstem lesions causing severe nausea, vomiting, or hiccups. Unlike prior diagnostic criteria, a positive anti-aquaporin-4 (AQP4) antibody test is not necessary for a diagnosis of NMOSD. Instead, current criteria add an additional qualifier for serological status describing whether a patient has a positive or negative anti-AQP4 serum antibody test.	Most patients (80%) diagnosed with NMOSD have anti-AQP4 antibodies. There may be differences in response to treatment and clinical outcomes in patients with NMOSD who have anti-AQP4 antibodies and patients with NMOSD who test negative for anti-AQP4 antibodies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Soliris (eculizumab), a monoclonal antibody targeting C5, and Uplizna (inebilizumab-cdon), a monoclonal antibody targeting CD19, are the only approved treatments for NMOSD in adult patients who are anti-AQP4 antibody positive. • Unapproved immunosuppressant therapies currently used to treat NMOSD have not been studied in adequate and well-controlled studies.	Soliris and Uplizna are the only approved treatments for NMOSD in adult patients who are anti-AQP4 antibody positive. Neither of these approved therapies for NMOSD is known to interact directly with the IL-6 receptor, the inhibitory target of satralizumab-mwge.
Benefit	• The applicant provides data from two double-blind, placebo-controlled time to event trials in a total of 171 adult patients with NMOSD with and without anti-AQP4 antibodies treated with satralizumab-mwge or placebo in which the primary outcome efficacy measure was the time to first confirmed relapse on trial. • Treatment with satralizumab-mwge significantly increased the time to a confirmed relapse in adult patients with NMOSD who were anti-AQP4 antibody positive with (p=0.0086), and without (p=0.0014) concurrent immunosuppressive treatments. • Treatment with satralizumab-mwge did not have a significant effect on the relative risk of relapse in patients who were anti-AQP4 antibody negative compared to placebo treatment in either study. • Treatment with satralizumab-mwge had no significant effect on standardized pain or fatigue scores in patients with NMOSD. • Findings in the seven patients below the age of 18 years old with NMOSD in Study 307JG were inadequate to support any efficacy	The data from the clinical trials provided in this application established the effectiveness of satralizumab-mwge for the treatment of NMOSD in adult patients who are anti-AQP4 antibody positive. The likelihood of experiencing a relapse was significantly reduced by 76-79% in patients treated with satralizumab-mwge who were anti-AQP4 positive regardless of whether patients were allowed to continue using other unapproved immunosuppressive therapies. There was no evidence of a clinical benefit for anti-AQP4 antibody negative patients in either study. The efficacy of satralizumab-mwge in patients less than 18 years old was not established.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	conclusions.	
Risk and Risk Management	• Patients treated with satralizumab-mwge experienced largely similar adverse events whether they were treated while continuing concurrent immunosuppression. The observed safety findings with satralizumab-mwge were consistent with those of tocilizumab, which is also a monoclonal anti-IL6 receptor antibody approved to treat rheumatoid arthritis and temporal arteritis. • There were no deaths in patients treated with satralizumab-mwge. • Serious potentially fatal infections, such as reactivation of hepatitis B and tuberculosis infections, have been cited as risks associated with other approved monoclonal antibody IL-6 receptor inhibitors (sarilumab and tocilizumab). There were no tuberculosis or hepatitis infections in Studies 307JG or 309JG. • The most common risks of treatment with satralizumab-mwge (15% or higher in either study and higher than placebo) were an increased risk of several types of infections (nasopharyngitis, upper respiratory tract infection), headache, gastritis, rash, arthralgia, extremity pain, fatigue, and nausea. • Injection reactions occurred approximately 3% more often in patients treated with satralizumab-mwge than placebo and were usually not serious.	The risks identified with satralizumab-mwge therapy appear manageable with labeling and monitoring. NMOSD is a serious, potentially fatal condition. An increased risk of serious infections is acceptable given the potentially fatal consequences of NMOSD without effective treatment. Other IL-6 receptor antagonists, sarilumab and tocilizumab, have boxed warnings for serious infections and potential reactivation of tuberculosis. The labeling of these approved therapies also warns of a potential for reactivation of hepatitis B infection. The clinical trials of satralizumab-mwge had no cases of hepatitis B nor tuberculosis because the trials excluded patients with these two diseases. A warning for serious infections, as well as adequate treatment of patients with prior histories of hepatitis B and tuberculosis will be included in labeling for satralizumab-mwge because the risks of reactivations of both

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Low neutrophil counts were associated with satralizumab-mwge treatment in both studies and led to discontinuation in one patient (<1% of all treated patients). • There were no known satralizumab-mwge exposures in pregnant women. In an animal reproduction study, there were no obvious adverse effects in offspring. The effects of satralizumab-mwge in pregnancy are unknown. • The safety findings in seven patients less than 18 years old randomized in Study 307JG were not adequate to support any safety conclusions for pediatric use of satralizumab-mwge. • Nonclinical data suggest offspring exposed to satralizumab-mwge in utero have a reduced response to novel antigens.	of these serious, potentially fatal infections are likely to be increased with satralizumab-mwge, too, given the shared mechanism of action between these three monoclonal anti-IL-6 receptor antibodies. The applicant will perform enhanced pharmacovigilance for serious infections in postmarketing. Decreased neutrophil counts, upper respiratory infections, headaches, nausea, gastritis, and joint and extremity pain are manageable conditions and amenable to monitoring. Higher rates of arthralgia and extremity pain have been noted in other NMOSD trials and do not appear to be treatment-specific findings for satralizumab-mwge. Labeling will advise of the potential fetal risk. A postmarketing pregnancy surveillance study will be required.

2. Background

This original biologics license application (BLA) contains data in support of the efficacy and safety of satralizumab-mwge, administered as a subcutaneous (SC) injection, for the proposed treatment of patients with neuromyelitis optica spectrum disorder (NMOSD).

NMOSD is a chronic disabling disease that is characterized by acute exacerbations, or relapses, in which patients experience inflammatory lesions within the central nervous system, most typically manifesting as optic neuritis or transverse myelitis. Relapses, also sometimes colloquially referred to as "attacks", can occur in one or both optic nerves, the spinal cord, the brainstem, and, less commonly, the brain. These relapses can result in blindness, weakness, paraplegia, loss of sensation, stroke-like symptoms, and bowel/bladder/sexual dysfunction. In rare instances when a lesion occurs in a region providing central respiratory drive or other critical functions, an NMOSD relapse can be fatal.

Most patients with NMOSD are women in their fourth decade of life, though NMOSD can be diagnosed in women or men at any age. NMOSD is considered to be a rare disease. The number of patients in the United States meeting current diagnostic criteria for NMOSD is estimated to be between 4,000 and 12,000 patients. Worldwide, there is considerable variability in the reported prevalence of NMOSD with broad differences observed based on geography and ethnicity. The prognosis for patients with NMOSD is historically viewed as poor. Most patients accumulate significant disability due to the cumulative effects of relapses. Estimates of mortality due to NMOSD-related sequelae range from 7-32%.

NMOSD is an autoimmune inflammatory disease and appears to be related to, in most cases, the production of antibodies that recognize the water channel protein aquaporin-4 (AQP4). In the spinal cord and optic nerve, AQP4 is one of the primary channels that permit water transit through the cell membrane; AQP4 is particularly concentrated on the end feet processes of astrocytes. Healthy individuals typically do not have antibodies directed against AQP4. The creation of anti-AQP4 antibodies appears to be a pathognomonic step in the acquisition of NMOSD. More than 50% of patients diagnosed with NMOSD will have a detectable titer of anti-AQP4 antibodies in their serum or spinal fluid.

Satralizumab-mwge is a humanized, IgG2 monoclonal antibody that binds to the interleukin-6 (IL-6) receptor. The binding of satralizumab-mwge at the IL-6 receptor

prevents binding of IL-6 and inhibits IL-6 receptor signaling. IL-6 is a pro-inflammatory cytokine secreted by leukocytes and other inflammatory cells that acts as mediator of fever production and is the primary activator of the production of acute phase proteins by the liver. Although IL-6 can act on targets other than its receptor, IL-6 signaling by activating the IL-6 receptor is critical to IL-6's roles in the inflammatory response and immunity. Pathological IL-6 dysregulation, associated with inappropriately prolonged secretion of IL-6 and high circulating IL-6 levels in serum, is hypothesized to play a role in many autoimmune diseases. Therefore, inhibition of IL-6 receptors as a means to interrupt IL-6 signaling is a potential treatment for autoimmune diseases. In 2010, based on demonstrated efficacy in the treatment of rheumatoid arthritis, Actemra (tocilizumab) became the first anti-IL-6 receptor monoclonal antibody approved to treat any autoimmune disease. Actemra is now also approved to treat several additional autoimmune diseases (giant cell arteritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis) as well as cytokine release syndrome, an immune condition associated with the use of chimeric antigen receptor T-cell therapies for individualized oncology treatment. Kevzara (sarilumab) was approved in 2017 to treat moderately or severely active rheumatoid arthritis that has had an inadequate response to other treatments. Thus, there are multiple lines of evidence that anti-IL6 receptor monoclonal antibody therapies are effective treatments for serious systemic autoimmune diseases.

There are two approved treatments for NMOSD. Soliris (eculizumab) was approved on June 27, 2019, for the treatment of adults with NMOSD who are anti-AQP4 antibody positive. Eculizumab is a monoclonal antibody that inhibits the cleavage of complement protein C5 and prevents the formation of the terminal complement complex. Uplizna (inebilizumab-cdon) was approved for the treatment of adults with NMOSD who are anti-AQP4 antibody positive on June 11, 2020. Inebilizumab-cdon is a monoclonal antibody that targets the CD19 antigen and selectively depletes B-cells from the serum. There are no approved therapies for NMOSD in patients who are negative for anti-AQP4 antibodies. There are no approved therapies for pediatric patients with NMOSD.

This application contains data from Study 307JG and Study 309JG, which were both prospective, randomized, placebo-controlled trials, as the basis of support for the safety and effectiveness of satralizumab-mwge in the treatment of NMOSD.

Dr. Lawrence Rodichok's clinical review provides the regulatory history of the development program for satralizumab-mwge for the treatment of NMOSD. This development program was granted fast track designation on October 31, 2013, was granted orphan drug designation for the treatment of NMOSD on June 30, 2014, and

was granted breakthrough therapy designation for the treatment of NMOSD on December 18, 2018 (prior to the approval of the first effective treatment for NMOSD, Soliris). Study 309JG was conducted under a Special Protocol Assessment (SPA) with an SPA agreement reached on October 17, 2014.

In November 2017, before completion of Study 309JG, the applicant reported to the Agency that it had become aware of internal attempts by biostatisticians employed by the applicant to use fibrinogen serum levels (which are reduced by satralizumab-mwge treatment) to predict treatment assignment and perform unauthorized interim efficacy analyses. These employees calculated estimated hazard ratios on two occasions based on assumed treatment assignments and had shared their findings with colleagues including treating investigators. During a teleconference held with the Agency on December 7, 2017, the applicant shared a mitigation plan with the Agency which included restriction of internal data access and independent data auditing. The Agency requested sensitivity analyses be conducted on data obtained before and after the internal attempts at unblinding, and the applicant agreed to submit those as part of a comprehensive bias report as part of the marketing application.

Currently, satralizumab-mwge is not approved or marketed for the treatment of any indication in the United States or elsewhere.

3. Product Quality

The Office of Biotechnology Products (OBP) provided an integrated review of product quality. The primary reviewer was Dr. Sang Bong Lee, and the team leader was Dr. Chana Fuchs. Refer to the OBP review for the entire listing of the review team by discipline. The OBP team recommends approval of this application.

The OBP review found no chemistry, manufacturing, and control (CMC)-related deficiencies in the application. The manufacturing process of satralizumab-mwge is well-controlled and leads to a pure, potent product.

The review states that the drug product is free from endogenous and adventitious infectious agents and meets the Agency's standards.

The review noted that the conditions used in the manufacturing process had been adequately validated. The review confirmed the applicant's stability assertions. The applicant's proposed shelf-life of (b) (4) months when stored at (b) (4) °C

for the drug substance, and drug product shelf-life of 24 months when stored at 2°C to 8°C, were both found to be acceptable.

The OBP review team found that the manufacturing facilities for the drug substance and drug product were both acceptable based on their current acceptable cGMP compliance status and recent relevant inspectional coverage.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. David Hawver. Dr. Lois Freed provided a supervisory review. Dr. Hawver recommends approval, and Dr. Freed concurs. The principal conclusions of Drs. Hawver's and Freed's reviews are as follows:

- An adequate battery of pharmacology studies was conducted to characterize the specificity, affinity, and pharmacological mechanism of action of satralizumab-mwge. The cynomolgus monkey was identified as the relevant species for study because satralizumab-mwge binds to the cynomolgus monkey IL-6 receptor. By prior agreement with the Division, there were no carcinogenicity nor mutagenicity studies conducted. The data confirm that satralizumab-mwge selectively binds to IL-6 membrane bound receptors and soluble IL-6 receptors and inhibits the activation of IL-6 receptors in both humans and cynomolgus monkeys.

- In vitro studies demonstrated that satralizumab-mwge selectively binds to the membrane bound and soluble IL-6 receptors. Satralizumab-mwge showed concentration-dependent inhibition of IL-6 receptor signaling in several monkey and human assays. Satralizumab-mwge binding did not cause antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) after binding to target cells.

- In vitro, satralizumab-mwge was shown to inhibit proliferation of peripheral human T-cells, reduce release of inflammatory cytokines from human cells, and decrease IL-6-induced production of immunoglobulin G (IgG) by human plasmablasts.

- In general toxicity studies in monkey, weekly subcutaneous doses of up to 50 mg/kg for 4 or 26 weeks resulted in no notable toxicity or effects on male (sperm analysis) and female (menstrual cycle) reproductive parameters and organs.

- In the enhanced pre- and postnatal development study in monkey, satralizumab-mwge (0, 2, and 50 mg/kg) was administered weekly to dams by subcutaneous injection from gestation day 20 to delivery. Offspring were followed to postnatal day 293. No adverse effects were observed on developmental parameters; however, impaired immune function in the T-cell dependent antibody reaction assay using keyhole limpet hemocyanin was observed in offspring at both doses.

- The nonclinical data in the application are sufficient to support approval, and labeling can address identified nonclinical findings adequately. There is no need for further nonclinical postmarketing toxicology studies such as a juvenile toxicology study because NMOSD is very rare in children. Further, satralizumab-mwge was granted orphan drug designation and thus is exempted from pediatric research equity act (PREA) study requirements.

5. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) provided an integrated review of this application. Drs. Dawei Li, Michael Bewernitz, and Manuela Grimstein were the primary reviewers, and Drs. Atul Bhattaram, Yuching Yang, and Angela Men were the team leaders. Dr. Mehul Mehta was the Division Director. The OCP team recommends approval.

Table 1, adapted from the OCP review, summarizes the conclusions of the OCP team with respect to the pharmacologic and clinical pharmacokinetic (PK) properties of satralizumab-mwge.

Table 1: General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Satralizumab-mwge is a humanized engineered monoclonal antibody that targets soluble and membrane-bound human IL-6 receptor and thereby prevents IL-6 downstream signaling through these receptors.
QT Prolongation	No formal QT evaluation has been conducted for satralizumab-mwge. As a large molecule, satralizumab-mwge has a

	low likelihood of directly interacting with ion channels.
General Information	
Bioanalysis	Satralizumab-mwge was measured in human serum using a validated Enzyme Linked Immunosorbent Assay (ELISA) method.
Drug Total Exposure Following the Therapeutic Dosing Regimen	Steady state pharmacokinetics were achieved after the loading period (8 weeks) for C_{min}, $C_{max,}$ and $AUC_{(0-t),}$ as follows: C_{min}: 19.7 (±12.2) mcg/mL, C_{max}: 31.5 (±14.9) mcg/mL, and $AUC_{(0-t)}$: 737 (±386) mcg.mL/day.
Dose Proportionality	The pharmacokinetics of satralizumab-mwge have been shown to be non-linear, with increased clearance at lower doses due to target-mediated drug disposition (TMDD). For single subcutaneous administrations of satralizumab-mwge ranging from 60 to 240 mg, the point estimates for the slopes of AUC_{inf} and C_{max} were 1.67 and 1.24, respectively.
Immunogenicity	Due to interference between satralizumab-mwge and the neutralizing antibody assay, assessment of neutralizing antibodies was not determined. Binding antibody measures are the only interpretable immunogenicity assessments in this submission. In NMOSD patients receiving the recommended treatment regimen, 52% of patients and 73% of patients developed anti-drug antibodies (ADAs) when satralizumab-mwge was given with concurrent immunosuppressant therapy (Study 307JG) and as monotherapy (Study 309JG), respectively. Lower satralizumab-mwge exposure was

	observed in ADA-positive patients, which was also associated with higher body weight. It is not clear whether the presence of ADA has a clinically-relevant impact on satralizumab-mwge efficacy. The development of ADA does not appear to have a clinically-relevant effect on the safety of satralizumab-mwge.
Inhibitor/Inducer Potential	As a monoclonal antibody inhibiting IL-6 signaling, the impact on CYP activity was investigated using physiologically based pharmacokinetic (PBPK) modeling and simulation. Although this analysis was considered exploratory, based on the low baseline IL-6 levels seen in NMOSD patients in the Phase 3 studies, the IL-6 mediated suppression of CYP enzymes is expected to be low. Accordingly, the impact of satralizumab-mwge treatment on the exposure of CYP substrates is expected to be minor. Other potential interactions (e.g., with transporters) are not expected.
Distribution	
Volume of Distribution	Estimated central and peripheral volume of distribution were 3.46 L and 2.07 L, respectively.
Elimination	
Terminal Elimination Half-life	Approximately 30 days with associated linear clearance of 0.0601 L/day.
Metabolism / Excretion	As a humanized IgG2 monoclonal antibody, satralizumab-mwge is expected to be degraded into small peptides and amino acids by proteolytic enzymes widely distributed in the body.

With effective inhibition of the IL-6 receptor using a monoclonal antibody, an increase in serum IL-6 is expected to occur through displacement of IL-6 from its native receptor. Also, soluble IL-6 receptor (sIL-6R) would be predicted to increase as a

compensation for reduced signaling through cell membrane-bound IL-6 receptors. All patients with NMOSD in Studies 307JG and 309JG who received satralizumab-mwge had significant, sustained increases in the mean levels of sIL-6R and IL-6 that paralleled the serum concentration of the monoclonal antibody. The OCP review also notes that C-reactive protein, C3, C4, and CH50 declined relative to placebo treatment to a constant value. Taken together, the OCP review concluded that the relationship between the treatment exposure and these pharmacodynamic (PD) markers showed strong evidence of engagement of the IL-6 receptor with reduced systemic inflammation. The OCP review noted that these PD findings were similar whether patients were treated with other immunosuppressants or not.

The OCP review noted that the use of a single dosing regimen in both trials precluded extrapolation of efficacy to other doses. Thus, the OCP team did not review the applicant's exposure-response analyses but agreed that the selected dosing regimen appeared effective based on the PD and clinical findings.

With respect to immunogenicity's impact on satralizumab-mwge efficacy and safety, the OCP review noted that patients who had ADAs tended to have higher body weights, lower satralizumab-mwge exposures, and higher IL-6 levels (but lower sIL-6R levels) than ADA-negative patients. The analyzed PD inflammatory markers, however, did not differ between ADA-positive and ADA-negative patients. A post hoc analysis supplied by the applicant suggested that ADA-negative patients had a reduced risk of relapse compared to ADA-positive patients (a group that disproportionately included above average weight patients) but the applicant noted that patients who have NMOSD and have higher body weight have a higher risk of a relapse independent of treatment. The applicant concluded that the observed association between ADA-positive patients and lower efficacy was spurious and was just a recapitulation of this established relationship between higher body mass and higher relapse risk known to occur in NMOSD. The OCP review could not make a definitive conclusion regarding ADA status and efficacy because of the potential confounding of above mean weight as an overall risk factor for higher relapse rates and because the PD markers did not all converge on a conclusive trend in the presence or absence of ADAs. There was no obvious impact on safety outcomes related to ADA status.

IL-6 is a potent activator of cytochrome P450 (CYP450) activity in the liver. Therefore, the OCP review addressed whether inhibition of IL-6 receptors by satralizumab-mwge suppressed endogenous CYP450 activity. A PBPK analysis and modeling supplied by the applicant did not demonstrate a significant effect attributable to satralizumab-mwge. However, the OCP review noted flaws with several assumptions

in the applicant's PBPK analyses. The OCP team conducted an in-depth survey of the medical literature that suggested clinically significant alterations in CYP450 activity might occur at IL-6 levels in the liver outside the range in the applicant's models. The OCP reviewer analysis suggested that the baseline serum IL-6 level in the patients might be a potential key factor for estimation of the potential interaction of satralizumab-mwge with CYP450 substrates, but this assertion was speculative because of a discrepancy between the IL-6 serum levels found in these two studies' patient populations and what has been reported in publications for IL-6 serum levels in the worldwide NMOSD population. Therefore, the OCP review concluded that the applicant's model of CYP450 interaction with satralizumab-mwge was reasonable but flawed, and their own hypothesis regarding the correlation of baseline serum IL-6 and CYP450 had plausibility but needed further validation. The OCP review could not conclude if there was an impact of satralizumab-mwge on CYP450 activity but their analysis did suggest that if such an effect existed it would not be large and would be unlikely to have clinical significance.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Lawrence Rodichok was the clinical reviewer for this application. Dr. Sharon Yan was the biometrics reviewer, Dr. Kun Jin was the team leader, and Dr. Jim Hung was the biometrics Division Director for this application.

Studies 307JG and 309JG

The applicant submitted findings from two adequate and well-controlled efficacy trials, Studies 307JG and 309JG, in support of this application. These multicenter, randomized, double-blind, placebo-controlled, parallel assignment studies were identical in most respects with the major differences being:

- Study 307JG allowed patients to remain on one of the following baseline treatments: azathioprine, mycophenolate mofetil, or oral corticosteroids. Study 309JG did not allow patients to be treated with any chronic immunosuppressive treatments during the trial.
- Study 307JG allowed enrollment of pediatric and adult patients. Study 309JG only enrolled adult patients.
- Study 309JG was conducted under an SPA agreement with the Division.

Inclusion Criteria

The inclusion criteria for Studies 307JG and 309JG were identical and were based on clinical criteria for "neuromyelitis optica" (NMO) as defined in publications by Wingerchuk in 2006. These criteria underwent significant revision after these trials began enrollment, and, among other changes, NMO was renamed "NMOSD." The enrollment criteria for Studies 307JG and 309JG were not altered to accommodate the changes in the international diagnostic criteria. However, because the changes in the international criteria expanded eligibility for diagnosis, the patients enrolled in Studies 307JG and 309JG who enrolled with a diagnosis of "NMO" would qualify under the revised criteria for a diagnosis of NMOSD. Thus, the enrolled populations in Studies 307JG and 309JG are representative of patients with the contemporary diagnosis of NMOSD.

Additionally, in the 2006 NMO diagnostic criteria, anti-AQP4 antibody status was a criterion that supported a diagnosis of NMO, with the presence of serum anti-AQP4 antibodies being consistent with the NMO diagnosis. Given the perceived importance of antibody status in confirming a diagnosis of NMO at the time of trial design, Studies 307JG and 309JG limited patients who were anti-AQP4 antibody negative to 30% of the total study population. In the current NMOSD criteria, antibody negative patients can have a diagnosis of NMOSD because anti-AQP4 antibody status is an additional disease descriptor and not essential for establishing a diagnosis. Including, but limiting the number of, anti-AQP4 antibody negative patients in these trials is not a factor in generalizability because, even with the revised criteria allowing negative patients to have an NMOSD diagnosis, the majority of patients diagnosed with NMOSD are anti-AQP4 antibody positive.

Relapse Assessment and Treatment

The primary outcome measure for Studies 307JG and 309JG was the same, the time to first on-trial independently confirmed relapse. A relapse was defined in the protocol as the occurrence of new or worsening neurological deficit attributable to a relapse persisting for more than 24 hours and not attributable to confounding clinical factors (e.g., fever, infection, injury, change in non-investigational treatment).

The criteria for a new or worsened neurologic deficit were:

- An increase of at least 1.0 point on the Expanded Disability Status Scale (EDSS) score excepting increase to 1.0 or 1.5 from zero (i.e., a 2.0-point increase on the EDSS was required if the baseline was zero)
- An increase of at least 2.0 points on one of the appropriate Functional Systems Score (FSS)

- An increase of at least 1.0 point on two or more of the appropriate FSS if the baseline score was one or more
- An increase of at least 1.0 point in single eye FSS when the baseline score in that eye is one or more

To provide confidence that relapses were evaluated in an unbiased manner, both of these studies used a standardized relapse assessment process with relapse determination ultimately confirmed by an independent committee. At the time a patient reported of signs and symptoms consistent with a potential relapse, the treating investigator requested that an EDSS/FSS assessment be performed by an independent examining assessor. The independent EDSS/FSS assessor had no access to the patient's clinical data. The treating investigator indicated in the relapse assessment form and the electronic case report form whether the relapse met the criteria for a protocol defined relapse. However, all cases of a potential relapse (a "clinical relapse") reported by the treating investigator during the double-blind period (irrespective of whether indicated as protocol defined relapse or not) were independently assessed by a panel of experts known as the Clinical Events Committee (CEC) to determine if the protocol defined relapse criteria were met. The CEC received a dossier consisting of the relapse assessment form, the EDSS and FSS scoring forms of the actual relapse assessment, and the preceding visit's assessment. The CEC was permitted to request additional information to assist in the determination of a relapse, if necessary. The CEC reviewed all cases of relapse and adjudicated each to see if it met the per protocol definition of a relapse. In order to ensure that no relapse events were missed, the adjudication process included a concurrent review of all clinical relapses noted in the trial. A protocol defined relapse that was confirmed by the CEC, and had an EDSS assessment within seven days of the initial report to the treating investigator, was treated as an outcome event for the purposes of the primary efficacy analysis.

At the time of a relapse, treatment with intravenous corticosteroids, intravenous immunoglobulin, plasma exchange, or plasmapheresis was permitted.

Key Secondary Endpoints

The key secondary endpoints of Studies 307JG and 309JG were:

- Analysis of change in Visual Analogue Score (VAS) for pain from baseline to week 24 using analysis of covariance (ANCOVA) with baseline observation carried forward (BOCF) methodology for imputation of missing values.

- Analysis of change in Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale score from baseline to Week 24 using ANCOVA with BOCF methodology for imputation of missing values.

Study 307JG Other Design Factors

In Study 307JG, approximately 70 adult (ages 18-74 years old) and 8 pediatric (ages 12-17) patients were to be randomized 1:1 to either subcutaneous satralizumab-mwge at 120 mg or matching subcutaneous placebo at Weeks 0, 2 and 4, and every 4 weeks thereafter, in combination with one of the following baseline treatments: azathioprine, mycophenolate mofetil, or oral corticosteroids. Pediatric patients were permitted to continue treatment with both oral corticosteroids and either azathioprine or mycophenolate mofetil. Randomization in Study 307JG was stratified by baseline annualized relapse rate and geographical region. Eligible patients were to be randomized at sites in Europe, Asia, and North America. For patients 12 to 17 years of age, enrollment was to continue until 8 patients had been enrolled or the study ended. The double-blind phase was to end when 26 CEC-confirmed relapses had occurred.

Study 309JG Other Design Factors

In Study 309JG, approximately 90 adult patients were to be randomized 2:1 to treatment with either subcutaneous satralizumab-mwge or subcutaneous placebo at Weeks 0, 2 and 4, and every 4 weeks thereafter. Concurrent use of immunosuppressive treatment was not permitted in this study. Randomization was stratified by prior therapy for prevention of NMOSD relapse (B-cell depleting therapy vs. other immunosuppressants or other therapies) and by the most recent relapse in the last one year prior to screening (first relapse). Patients were treated to the time of a confirmed relapse or until the end of the randomized-controlled phase (RCP) of the trial. The end of the double-blind period was defined as the date when the total number of relapses reached 44 or 1.5 years after the date of randomization of the last patient enrolled, whichever occurred first.

Results

Study 307JG

Demographics

The intention-to-treat (ITT) population for Study 307JG comprised 83 randomized patients who received at least one dose of satralizumab-mwge (n=41) or placebo treatment (n=42). Of these 83 patients, 52 were positive for anti-AQP4 antibodies, and 31 were negative for anti-AQP4 antibodies. There were seven pediatric patients and 76 adult patients in this trial. An eighth pediatric patient was enrolled in the trial the

day before the clinical cut-off date and was not included in the ITT because this patient was neither randomized nor treated before the study concluded.

The ITT population in this study, aside from the seven pediatric patients, was generally consistent with the reported demographics of NMOSD. Almost all (93%) of the randomized patients were women, the mean age was 45.6 years old (median age was 45.5 years old), and over 98% were White or Asian. Demographic characteristics were generally balanced between the two treatment groups. There were no obvious demographic differences between the anti-AQP4 positive and negative populations.

Primary Outcome Measure
During the trial, 45 patients experienced an event consistent with a clinical relapse.

Treating investigators identified 27 patients in the placebo treatment group who experienced potential on-trial relapses. The CEC confirmed a protocol-defined relapse had occurred in 18/27 (67%) of these patients.

Treating investigators identified 18 patients in the satralizumab-mwge treatment group who experienced a potential on-trial relapse. The CEC confirmed a protocol-defined relapse had occurred in 8/18 (44%) of these patients.

In Study 307JG, placebo-treated patients had a higher frequency of relapses, and, because patients experiencing relapses exited the trial, patients treated with placebo spent less time in the double-blind portion of the trial. The median duration of time in the double-blind phase of Study 307JG for patients treated with placebo was 43 weeks (range: 8-185 weeks). Patients treated with satralizumab-mwge had a median in-trial duration of 115 weeks (range: 10-224 weeks).

The following table, adapted from the biometrics review, presents the results of the primary efficacy analysis:

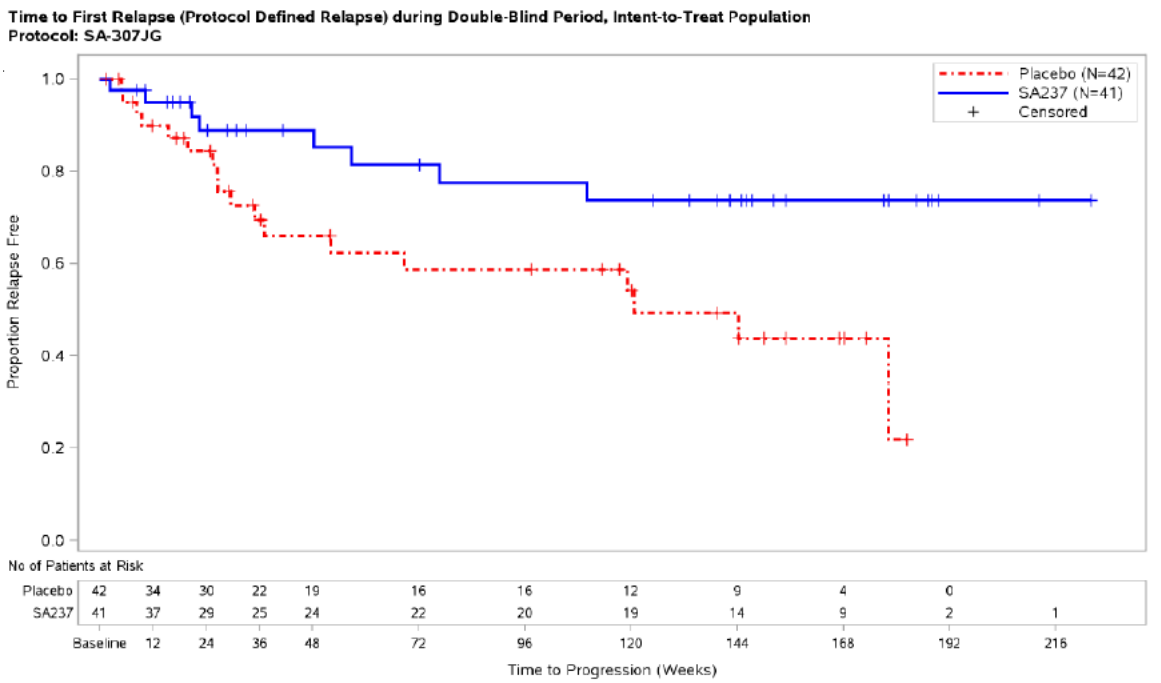
Table 2: Study 307JG: Analysis of Time to CEC-Confirmed NMOSD Relapses, ITT Population

	Placebo N=42	Satralizumab-mwge N=41
Number (%) of Patients with CEC-Confirmed Protocol Defined Relapse	18 (42.9%)	8 (19.5%)
Time to Initial CEC-Confirmed Protocol Defined Relapse		
Primary Analysis (log-rank test) p-value		 0.0184
Secondary Analysis (Cox model) Hazard Ratio Satralizumab-mwge/Placebo 95% Confidence Interval (CI) p-value		 0.38 (0.16, 0.88) 0.0231

Source: Biometrics Review, Table 4

The following figure, copied from the biometrics review, presents the Kaplan-Meier estimate to first CEC-confirmed relapse for the ITT population in Study 307JG.

Figure 1: Study 307JG: Kaplan-Meier Curves for Time to CEC-Confirmed NMOSD Relapses, Applicant's ITT Population



Source: Biometrics Review, Figure 3

The primary efficacy outcome analysis of Study 307JG, confirmed by the biometrics reviewer, was statistically significant (p=0.0184) overall in favor of satralizumab-mwge (designated "SA237" in the figure legend). The treatment effect of satralizumab-mwge is evident before 12 weeks of treatment. A secondary analysis also confirmed by the biometrics reviewer using a Cox proportional hazards model replicated the significant primary analysis finding (p=0.0231).

The applicant provided four sensitivity analyses as follows: log-rank tests of time to first relapse for CEC-confirmed relapses regardless of an EDSS assessment obtained within a window of seven days of reported onset, all clinical relapses, all treated clinical relapses, and treated episodes of optic neuritis. The biometrics reviewer confirmed these sensitivity analyses' findings. The only sensitivity analysis to reproduce the primary analysis's significant result was the log-rank test of time to first relapse for CEC-confirmed relapses, irrespective of when EDSS assessment was obtained (hazard ratio=0.41, p=0.0304). The biometrics and clinical review note that the higher rate of CEC confirmation of clinical relapses in the placebo treatment group was the reason for the lack of recapitulation of the primary outcome analysis in three of the four sensitivity analyses. A higher rate of confirmation of relapses in placebo-treated patients was noted in two other NMOSD development programs that used independent bodies to confirm relapses and is not unique to this development program.

The applicant performed subgroup analyses to examine the effects of age (under age 18/greater than or equal to 18 years old), race (Japanese/non-Japanese), Region (Asia, Europe/other), baseline annualized relapse rate (1/greater than 1), diagnosis with anti-AQP4 status (NMO/NMOSD and anti-AQP4 positive/negative), baseline treatment (azathioprine, mycophenolate mofetil, or oral corticosteroids), and anti-AQP4 antibody status.

Anti-AQP4 Antibody Status

In the applicant's pre-planned subgroup analysis that evaluated the ITT population with respect to anti-AQP4 antibody status, a highly significant treatment effect on relapses of satralizumab-mwge was noted only in anti-AQP4 antibody positive patients (p=0.0086). The percentage of anti-AQP4 antibody negative patients experiencing a CEC-confirmed relapse was nearly identical in the placebo and active treatment groups (14.3% and 12.2%), and the hazard ratio for antibody negative patients was over three-fold higher than that of antibody positive patients. This subgroup analysis failed to demonstrate a significant effect of treatment in the patients who were negative for anti-AQP4 antibodies (p=0.5047), and the overall result in the ITT population's significant treatment response was attributable to the

robust effect in the anti-AQP4 antibody positive patients as indicated in the following table:

Table 3: Study 307JG: Analysis of Time to CEC-Confirmed NMOSD Relapses, ITT Population with AQP4 Antibody Status

	Placebo N=42		Satralizumab-mwge N=41	
	Anti-AQP4 Positive n=28	Anti-AQP4 Negative n=14	Anti-AQP4 Positive n=27	Anti-AQP4 Negative n=14
Number (%) of Patients with CEC-Confirmed Protocol Defined Relapse	12 (28.6%)	6 (14.3%)	3 (7.3%)	5 (12.2%)
Hazard Ratio Satralizumab-mwge/Placebo* 95% Confidence Interval p-value			0.21 (0.06, 0.75) 0.0086	0.66 (0.20, 2.24) 0.5047

*Cox model
Source: Biometrics review, Table 11

Drs. Rodichok and Yan concluded that the results for the anti-AQP4 antibody negative patients, when considered separately from the overall ITT population's findings, provided no evidence of effectiveness. The primary outcome analyses provide evidence of a significant treatment effect on relapses for anti-AQP4 antibody positive patients but do not provide evidence of a treatment effect on relapses in anti-AQP4 antibody negative patients.

Baseline Treatment
Study 307JG allowed adult patients to remain on concurrent baseline immunosuppressive treatment with azathioprine, mycophenolate mofetil, or oral corticosteroids.

Table 4: Study 307JG: Analysis of Time to CEC-Confirmed NMOSD Relapses, ITT Population with Baseline Treatments

	Total (N=83)	Placebo (N=42)		Satralizumab-mwge (N=41)		Hazard Ratio (95% CI)	p-value
	N	n	CEC-confirmed Relapses	n	CEC-confirmed Relapses		
Azathioprine	29	13	7	16	5	0.621 (0.188, 2.051)	0.4307
Mycophenolate Mofetil	12	8	2	4	1	0.00 (0.00, --)	0.1025
Oral Corticosteroids	37	20	8	17	1	0.152 (0.018, 1.253)	0.0462

Source: Study 307JG CSR, Figure 5

The results of this subgroup analysis suggest a trend effect (nominal p=0.0462) for a benefit of satralizumab-mwge treatment in patients in the overall ITT population who continued to take oral corticosteroids, but the overall treatment effect of satralizumab-mwge is not recapitulated for patients taking azathioprine or mycophenolate mofetil. However, there are several issues with this analysis that render its findings difficult to interpret. Study 307JG was not adequately designed to assess satralizumab-mwge as an "add-on" therapy to specific individual agents, and the numbers of patients using the three treatments were not balanced. This study was not powered adequately to generate a statistically robust finding for the baseline treatment variable. None of these three baseline immunosuppressive therapies have been demonstrated in adequate, well-controlled trials to be effective in the treatment of NMOSD relapses; it is possible that these treatments interact with the beneficial effects of satralizumab-mwge. Finally, this subgroup analysis was not corrected for multiplicity, and so these results may represent spurious statistical outcomes.

Pediatric Patients

There were seven pediatric patients (patients younger than 18 years old) enrolled in Study 307JG; four of these patients were randomized to satralizumab-mwge treatment. The overall primary analysis of these pediatric patients was not significant (hazard ratio=0.00, p=0.1573). Three of these pediatric patients were anti-AQP4 antibody positive, two were randomized to placebo treatment and one to

satralizumab-mwge treatment. One anti-AQP4 antibody positive patient in each treatment arm experienced a CEC-confirmed relapse; thus there was no obvious basis to discern a treatment effect in the anti-AQP4 antibody positive pediatric patients as had been the case in adult antibody positive patients. Dr. Rodichok concluded that, because of the small sample size and paucity of events, there was insufficient evidence to support any meaningful conclusions regarding effect of treatment in patients less than 18 years old.

Other Subgroup Analyses

The subgroup analyses for race, region, baseline annualized relapse rate, and diagnosis with anti-AQP4 status were generally consistent with the overall primary outcome finding in the ITT population, with a significant treatment effect of satralizumab-mwge restricted to anti-AQP4 antibody positive patients. These subgroup analyses were confirmed by the biometrics reviewer who concurred with the applicant's findings.

Secondary Outcome Measures

The secondary outcome measures of Study 307JG were as follows, in hierarchical order: change from Baseline to Week 24 in the VAS for pain and the FACIT Fatigue Scale. The primary analysis of these secondary endpoints used a baseline observation carry-forward (BOCF) method to impute missing values.

Changes in VAS and FACIT

The following table, copied from the biometrics review, presents the results of the analysis of changes in VAS and FACIT Fatigue Score from baseline to week 24

Table 5: Study 307JG: Changes in VAS Pain and FACIT Fatigue Scores from Baseline to Week 24, ITT

	Placebo N=42	Satralizumab-mwge N=41
VAS		
Baseline		
N	42	41
Mean (Standard Error)	34.62 (26.09)	27.56 (28.17)
Change from Baseline to Week 24 (BOCF)		
N (imputed)	42	41
N (actual observed)	29	29
Adjusted Mean (95% CI)	-3.51 (-8.20, 1.19)	2.87 (-1.89, 7.62)
Adjusted Mean Difference (95% CI)		6.38 (-0.28, 13.03)
p-value (BOCF)		
p-value (actual observed)		0.0602 0.0932
FACIT Fatigue Scale		
Baseline		
N	42	41
Mean	33.85 (11.31)	34.73 (10.54)
Change from Baseline to Week 24 (BOCF)		
N (imputed)	42	41
N (actual observed)	29	29
Adjusted Mean (95% CI)	2.23 (0.36, 4.11)	0.14 (-1.77, 2.06)
Adjusted Mean Difference (95% CI)		-2.09 (-4.75, 0.57)
p-value (BOCF)		0.1224
p-value (actual observed)		0.0983

Source: Biometrics review, Table 5

The primary pre-specified analyses of the VAS and FACIT assessments were not statistically significant (p=0.0602 and 0.1224, respectively). Drs. Yan and Rodichok noted that VAS pain scores trended to higher numbers indicating increased pain at week 24 in patients treated with satralizumab-mwge. Dr. Yan noted in her review that there were a large number of patients without VAS and FACIT assessments at Week 24 because of patients exiting the study due to a relapse or discontinuation before week 24. Thus, she concluded the study was not ideally designed to fully capture a change from baseline in either outcome because the study population was small from

the outset and there would be an expected non-trivial attrition of patients from both treatment arms before Week 24 due to relapses. Therefore, the secondary outcome measure analyses had to rely on imputation methods to compensate. Since imputation using BOCF can bias outcome assessments, Dr. Yan performed analyses without imputation (using the actual number of observed 24-week outcome assessments, 29 in each treatment group). Her exploratory analyses for VAS and FACIT outcomes without BOCF also failed to achieve significance (p=0.0932 and p=0.0983, respectively).

Study 309JG

Demographics

The ITT population for Study 309JG comprised 95 randomized adult patients who received at least one dose of satralizumab-mwge (n=63) or placebo (n=32) treatment. Of these 95 patients, 64 were positive for anti-AQP4 antibodies, and 31 were negative for anti-AQP4 antibodies. There were no pediatric patients enrolled and patients were not allowed to use other chronic immunosuppressant medications during this trial.

The ITT population in this study was consistent with the reported demographics of NMOSD. Most (81%) of the randomized patients were women, the mean age was 43.7 years old (median age was 45.0 years old), and approximately 77% were White or Asian. Demographic characteristics were generally balanced between the two treatment groups with some minor discrepancies attributable to chance and unlikely to impact efficacy assessment. The demographics of the ITT population and the anti-AQP4 positive subpopulation of the ITT were similar; the anti-AQP4 positive and negative subpopulations were also similar to one another.

Primary Outcome Measure

During the trial, 48 patients, 17 in the placebo group and 31 in the satralizumab-mwge group, experienced events consistent with a clinical relapse (randomization was unequal, as noted above).

In the placebo treatment group, the CEC confirmed a protocol-defined relapse had occurred in 16/17 (94%) of these patients.

In the satralizumab-mwge treatment group, the CEC confirmed a protocol-defined relapse had occurred in 21/31 (68%) of patients with clinical relapses. Only 19 of these 21 CEC-confirmed relapses were included in the primary outcome analysis; two relapses were excluded from the primary analysis because the EDSS assessments for these events occurred more than seven days after symptom onset.

In Study 309JG, placebo-treated patients had a higher frequency of relapses, and, because patients experiencing relapses exited the trial, placebo-treated patients spent less time in the double-blind portion of the trial. The median duration of time in the double-blind phase of Study 309JG for patients treated with placebo was 60.5 weeks (range: 7-219 weeks). Patients treated with satralizumab-mwge had a median in-trial duration of 95.4 weeks (range: 8-205 weeks).

The following table, adapted from the biometrics review, presents the results of the primary efficacy analysis:

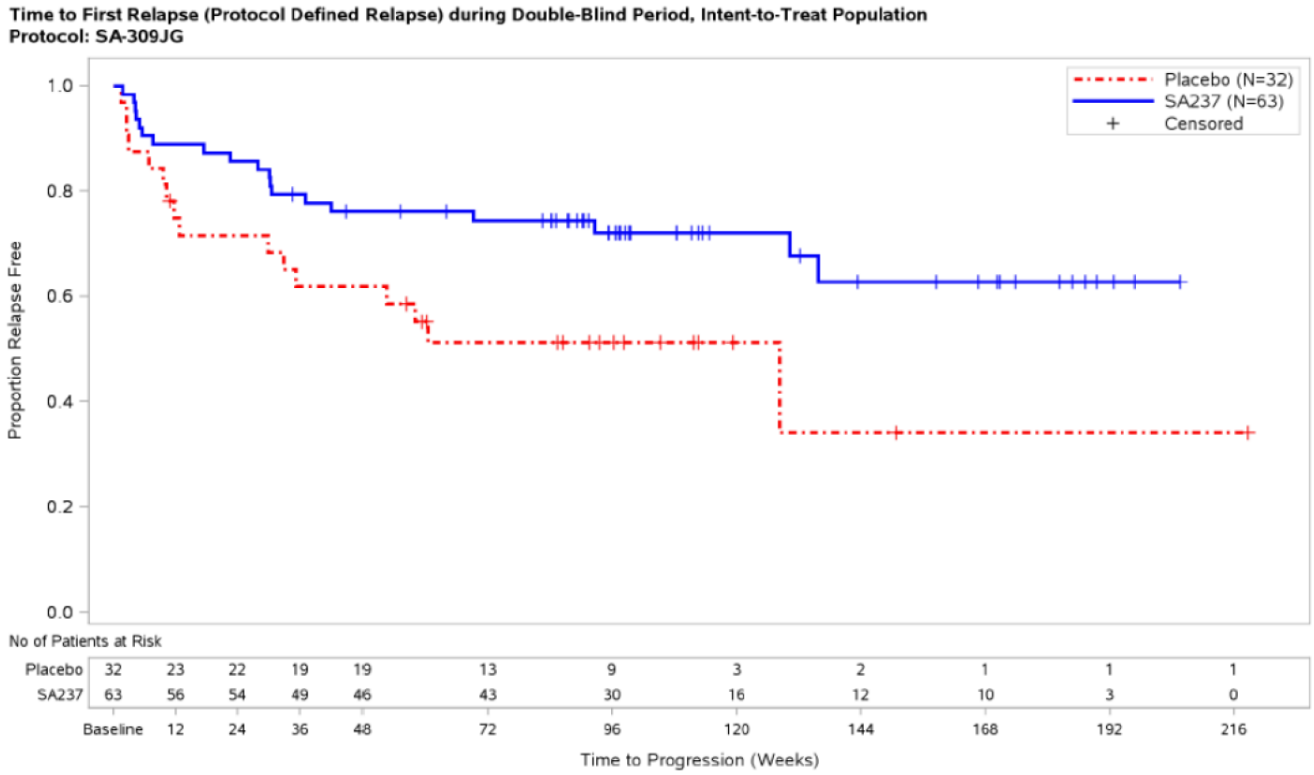
Table 6: Study 309JG: Analysis of Time to CEC-Confirmed NMOSD Relapses, ITT Population

	Placebo N=32	Satralizumab-mwge N=63
Number (%) of Patients with CEC-Confirmed Protocol Defined Relapse	16 (50.0%)	19 (30.2%)
Time to Initial CEC-Confirmed Protocol Defined Relapse		
Primary Analysis (log-rank test) p-value		 0.0184
Secondary Analysis (Cox model) Hazard Ratio Satralizumab-mwge/Placebo 95% Confidence Interval p-value		 0.45 (0.23, 0.89) 0.0215

Source: Biometrics Review, Table 8

The following figure, copied from the biometrics review, presents the Kaplan-Meier estimate to first CEC-confirmed relapse for the ITT population in Study 309JG.

Figure 2: Study 309JG: Kaplan-Meier Curves for Time to CEC-Confirmed NMOSD Relapses, Applicant's ITT Population



Source: Biometrics Review, Figure 6

The primary efficacy outcome analysis of Study 309JG, confirmed by the biometrics reviewer, was statistically significant (p=0.0184) overall in favor of satralizumab-mwge (designated "SA237" in the figure legend). The treatment effect of satralizumab-mwge is evident not long after initiation of treatment. A secondary analysis also confirmed by the biometrics reviewer using a Cox proportional hazards model replicated the significant primary analysis finding (p=0.0215).

The applicant provided four sensitivity analyses of this primary outcome assessment as follows: log-rank tests of time to first relapse for CEC-confirmed relapses regardless of an EDSS assessment obtained within a window of 7 days of reported onset, all clinical relapses, all treated clinical relapses, and treated episodes of optic neuritis. The biometrics reviewer confirmed these sensitivity analyses' findings. Two of these sensitivity analyses replicated the statistical significance of the primary outcome measure result, the log-rank tests of all treated clinical relapses (hazard ratio=0.46, p= 0.0186), and the time to first relapse for CEC-confirmed relapses, irrespective of when EDSS assessment was obtained (hazard ratio=0.49, p= 0.0336).

The applicant performed subgroup analyses to examine the effects of age (greater than 42 years old, less than or equal to 42 years old), race (Japanese/non-Japanese), Region (Asia, Europe/other, North America), diagnosis with anti-AQP4 status

(NMO/NMOSD and anti-AQP4 positive/negative), prior therapies (B-cell depleting therapy or other immunosuppressants), and anti-AQP4 antibody status.

Anti-AQP4 Antibody Status

In the applicant's pre-planned subgroup analysis that evaluated the ITT population of Study 309JG with respect to anti-AQP4 antibody status, a highly significant treatment effect on relapses of satralizumab-mwge was confined to positive patients (p= 0.0014). This subgroup analysis failed to demonstrate a significant effect of treatment in the patients who were negative for anti-AQP4 antibodies (hazard ratio=1.19, p=0.8036), and the overall result in the ITT population's significant treatment response was clearly driven by a robust effect in the anti-AQP4 positive patients as indicated in the following table:

Table 7: Study 307JG: Analysis of Time to CEC-Confirmed NMOSD Relapses, ITT Population with AQP4 Antibody Status

	Placebo N=32		Satralizumab-mwge N=63	
	Anti-AQP4 Positive n=23	Anti-AQP4 Negative n=9	Anti-AQP4 Positive n=41	Anti-AQP4 Negative n=22
Number (%) of Patients with CEC-Confirmed Protocol Defined Relapse	13 (40.6%)	3 (9.4%)	9 (14.3%)	10 (15.9%)
Hazard Ratio Satralizumab-mwge/Placebo* 95% Confidence Interval p-value			0.26 (0.11, 0.63) 0.0014	1.19 (0.30, 4.78) 0.8036

*Cox model

Source: Biometrics review, Table 11

Drs. Rodichok and Yan concluded that the results for the anti-AQP4 antibody negative patients, when considered separately from the overall ITT population's findings, provided no evidence of effectiveness and, with a hazard ratio greater than 1, trended toward a potential for increasing the likelihood of relapse associated with satralizumab-mwge treatment. The primary outcome analyses provide evidence of a significant treatment effect on relapses for anti-AQP4 positive patients but do not provide evidence of a treatment effect on relapses in anti-AQP4 negative patients.

Other Subgroup Analyses

The confirmed subgroup analyses of Study 309JG for age, race, region, prior immunosuppressive treatments, and diagnosis with anti-AQP4 status confirmed the overall primary outcome finding in the ITT population, with a significant treatment effect of satralizumab-mwge restricted to anti-AQP4 antibody positive patients. These subgroup analyses were confirmed by the biometrics reviewer who concurred with the applicant's findings.

Secondary Outcome Measures

The secondary outcome measures of Study 309JG were as follows, in hierarchical order: change from Baseline to Week 24 in the VAS for pain and the FACIT Fatigue Scale. The primary analysis of these secondary endpoints used a baseline observation carry-forward (BOCF) method to impute missing values.

Changes in VAS and FACIT

The following table, copied from the biometrics review, presents the results of the analysis of changes in VAS and FACIT Fatigue Score from baseline to Week 24.

Table 8: Study 309JG: Changes in VAS Pain and FACIT Fatigue Scores from Baseline to Week 24, ITT

	Placebo N=32	Satralizumab-mwge N=63
VAS		
Baseline		
N	32	62
Mean (Standard Error)	27.56 (30.76)	31.66 (28.86)
Change from Baseline to Week 24 (BOCF)		
N (imputed)	32	62
N (actual observed)	20	52
Adjusted Mean (95% CI)	-5.95 (-15.55, 3.65)	-2.73 (-11.20, 5.73)
Adjusted Mean Difference (95% CI)		3.21 (-5.09, 11.52)
p-value (BOCF)		0.4436
p-value (actual observed)		0.4321
FACIT Fatigue Scale		
Baseline		
N	32	62
Mean	29.66 (12.90)	30.59 (11.74)
Change from Baseline to Week 24 (BOCF)		
N (imputed)	32	62
N (actual observed)	20	53
Adjusted Mean (95% CI)	3.60 (-0.01, 7.22)	5.71 (2.51, 8.91)
Adjusted Mean Difference (95% CI)		2.11 (-1.01, 5.22)
p-value (BOCF)		0.1824
p-value (actual observed)		0.5585

Source: Biometrics review, Table 5

As had been the case in Study 307JG, in Study 309JG, the primary pre-specified analyses of the VAS and FACIT assessments were not statistically significant. Drs. Yan and Rodichok noted that adjusted mean pain scores again trended to higher values in patients treated with satralizumab-mwge, indicating increased pain at week 24. As in Study 307JG, the applicant relied on imputation with BOCF methods that could bias outcomes. Dr. Yan again performed analyses without imputation (using the actual number of observed 24-week outcome assessments); these exploratory analyses for VAS and FACIT outcomes using actual observed values also failed to achieve significance (p=0.4321 and p=0.5585, respectively).

Study 307JG and 309JG Bias Assessment

The applicant had reported to the Agency there had been two internal attempts to use serum fibrinogen levels (which are reduced by satralizumab-mwge treatment) to predict treatment assignment and conduct unauthorized interim efficacy analyses (see Section 2). These speculative efficacy analyses had been presented to members of the investigational team and therefore could have influenced the conduct of these studies. After consultation with the Agency prior to submission, the applicant agreed to include in the application a bias assessment including a discussion and analyses to assess whether these two attempts to use laboratory data to unblind Studies 307JG and 309JG had introduced significant bias into the data.

The applicant performed an analysis using just fibrinogen serum levels (as the unauthorized team members had done) and found that serum fibrinogen values available at the times of these efficacy interim assessments predicted treatment assignment 73.3%-100%. Thus, the applicant acknowledged that treating investigators who had seen these findings could have used this knowledge to bias outcome assessments. However, analyses of data collection sensitive to bias such as EDSS and the secondary outcome measure assessments revealed no differences in data collected before and after the two internal unblinding events. The biometrics reviewer agreed with the applicant's numerical analyses to assess bias and that the integrity of the primary and secondary outcome scores Studies 307JG and 309JG appeared intact and free of obvious bias despite the internal unblinding attempts.

Another source of concern were amendments to the SPA agreement for Study 309JG being influenced by bias from these internal unblinding efforts. The clinical/biometrics? reviewer noted in particular an SPA amendment that was submitted March 9, 2016, after the initial internal attempt (in November 2015) to unblind the trial had been made. This protocol change increased the sample size and number of events needed to end Study 309JG. Had the original protocol for Study 309JG, which had planned to enroll 70 patients and ended with 19 relapses events, remained in effect, the study's primary outcome analysis using data available at this time would have failed to show a treatment effect (hazard ratio=0.58 and p-value of 0.2413). The justification for the SPA amendment offered by the applicant at the time had been a higher early relapse rate than expected based on a pre-planned blinded data futility review. Though the applicant asserted the SPA amendment in March 2016 was not influenced by the initial internal unblinding attempt, the biometrics and clinical reviewers could not conclude definitively whether the protocol change had been in direct response to the internal unblinding attempts but did note there were other plausible reasons to make these changes to the SPA for Study 309JG. There was

no evidence other than coincidence that this SPA amendment had been influenced by the internal unblinding.

A second SPA amendment for Study 309JG, proposing to end the trial before the 44th clinical relapse had occurred, was submitted on July 10, 2018, after Study 307JG had been completed and after there had been a second internal attempt at unblinding the Study 309JG data which occurred in June 2017. This SPA amendment was advanced in an effort to minimize bias from availability of the completed Study 307JG outcomes and because of a longer than anticipated time to acquire the final relapses needed to complete the Study 309JG. Given the minimal impact of this amendment on the trial outcome (the study had achieved 43 relapses at the time of this submission, and so loss of a single relapse would be unlikely to impact the trial results significantly), this amendment appears highly unlikely to have been the result of influence by the internal unblinding.

Conclusions on Substantial Evidence of Effectiveness

The efficacy results from Studies 307JG and 309JG both demonstrate a significant treatment effect of satralizumab-mwge on relapses in NMOSD as compared to placebo. Subgroup analyses of these studies' findings provide support only for the approval of satralizumab-mwge for the treatment of NMOSD in adult patients who are anti-AQP4 positive. In these two trials, satralizumab-mwge significantly reduced the relative risk of relapse in anti-AQP4 antibody positive patients by 79% (nominal p=0.0086) and 76% (nominal p=0.0014), respectively, when compared to placebo treatment. The efficacy findings in the anti-AQP4 antibody positive populations from studies with and without other concurrent immunosuppression therapies were similar.

The primary efficacy outcome findings from Studies 307JG and 309JG did not provide any evidence of effectiveness in analyses of patients who are anti-AQP4 antibody negative (hazard ratios= 0.21 and 0.26, nominal p=0.5047 and p=0.8036, respectively). There were no differences in the demographics or baseline disease characteristics (other than anti-AQP4 antibody status) for antibody negative patients that distinguished them from the anti-AQP4 antibody positive patients and could explain the lack of observed efficacy. Satralizumab-mwge will therefore be indicated only for the treatment of patients with NMOSD who are anti-AQP4 positive.

This is the second NMOSD development program to demonstrate a marked difference in efficacy between anti-AQP4 antibody positive and antibody negative patients (the other development program for an approved NMOSD therapy studied

only anti-AQP4 antibody positive patients). The reason for this discrepancy is unknown but may reside in fundamental pathophysiological differences between the antibody negative and antibody positive patients in NMOSD that is heralded by anti-AQP4 antibody status.

Study 307JG enrolled seven patients less than 18 years old. The overall primary analysis of the time to first relapse in these seven patients revealed a hazard ratio=0 that was not statistically significant (p=0.1573). Less than half (n=3) of these seven pediatric patients were anti-AQP4 antibody positive (the group presumably more likely to have a treatment effect given significant findings in adults). There were two CEC-confirmed relapses in anti-AQP4 antibody positive patients, one occurring in a patient in each treatment arm. The equivocal findings in these seven patients, and in the smaller subgroup of three antibody-positive patients, are not sufficient to support any conclusions regarding efficacy in pediatric patients.

Treatment with satralizumab-mwge conferred no apparent benefit on key secondary endpoints measuring pain and fatigue in patients with NMOSD.

8. Safety

Dr. Lawrence Rodichok conducted the clinical safety review of Studies 307JG and 309JG, as well as the available data from the open-label extension phases of these studies. His review noted that there were 166 patients with NMOSD who were exposed to at least one dose of satralizumab-mwge in the applicant's NMOSD development program. Of these 166 patients, there were 104 patients who initially were randomized to receive satralizumab-mwge in the controlled portions of Studies 307JG and 309JG, with the remainder of the patients being those patients who were initially randomized to placebo but subsequently received satralizumab-mwge during open-label extension studies. Dr. Rodichok also reviewed safety data obtained in a small multiple ascending dose trial using satralizumab-mwge in patients diagnosed with rheumatoid arthritis; he found no additional safety signals to inform the NMOSD safety experience. Finally, there are two monoclonal antibody therapies which antagonize the IL-6 receptor (tocilizumab and sarilumab), and which each have years of postmarketing experience of use in patients with systemic autoimmune diseases, that can further inform the safety observed with satralizumab-mwge in patients with NMOSD.

The following table, copied from Dr Rodichok's review, summarizes the extent of exposure to satralizumab-mwge in the applicant's development program:

Table 9: Duration of Exposure in NMOSD Patients for Satralizumab-mwge

All Exposed	Mean Exposure	Standard Deviation	Minimum Exposure	Maximum Exposure	Median Exposure
N=166	2.6 years	1.4 years	0.2 years	5.3 years	2.5 years

Source: Clinical Review, Table 63

As indicated in the previous table, at the time of the safety update to the application, there were 166 patients with a median exposure to satralizumab-mwge of 2.5 years. In the overall safety population, most of the patients (87%) were women and over 86% were either White or Asian, which conforms approximately to the expected demographics for a NMOSD population recruited worldwide. In the safety population, 119 (72%) patients were anti-AQP4 antibody positive. Dr. Rodichok concluded that the safety databases for NMOSD, and for the subgroup of NMOSD patients with anti-AQP4 antibodies, were small but adequate to support meaningful conclusions.

Deaths

There were no deaths in patients treated with satralizumab-mwge in either Study 307JG or Study 309JG.

Serious Adverse Events

Study 307JG

The incidence of serious adverse events (SAEs) was 21.4% (12 SAEs in 9/42 patients) in the placebo group and 17.1% (8 SAEs in 7/41 patients) in the satralizumab-mwge group. When only anti-AQP4 antibody positive patients were considered, the incidence rates for SAEs in both treatment groups were an identical 27% (7/26 patients). Dr. Rodichok noted that the SAEs in the satralizumab-mwge treatment arm were all single events (macrocytic anemia, pneumonia, urinary tract infection, femur fracture, spinal compression fracture, tension headache, suicide attempt, and cervical dysplasia) without a clear identifiable pattern of treatment-associated specific risks. While there are two serious infections, there are also two events consistent with osteoporosis secondary to chronic corticosteroid use (femur and spinal compression fractures), which suggests that the use of concurrent immunosuppressants (especially corticosteroids) permitted in Study 307JG complicate this study's safety conclusions for satralizumab-mwge.

Study 309JG

The incidence of SAEs was 15.6% (5 SAEs in 5/32 patients) in the placebo group and was 19.1% (19 SAEs in 12/63 patients) in the satralizumab-mwge group. When only anti-AQP4 antibody positive patients were considered, the incidence rate for SAEs was 13.0% (3/23 patients) in the placebo treatment arm and was 17.1% (7/41 patients) in the satralizumab-mwge treatment arm. An analysis of SAEs limited to just anti-AQP4 antibody positive patients did not change the overall safety conclusions. The SAEs in the satralizumab-mwge treatment arm included two cases of mental status change and two cases of influenza infection. Otherwise, the reported SAEs were isolated events (radius fracture, pyelonephritis, pulmonary sepsis, urosepsis, apnea, bradycardia, enterocolitis, hypothermia, acute myocardial infarction, visual impairment, nausea, non-cardiac chest pain, pneumonia, and pulmonary edema). Seven infectious SAEs occurred in the satralizumab-mwge arm as opposed to two infections in the placebo arm. Since Study 309JG did not allow other immunosuppression treatment as Study 307JG did, this difference in observed serious infections in Study 309JG is more interpretable as a likely treatment-emergent effect of satralizumab-mwge. While placebo treatment durations were shorter, an exploratory analysis by patient-years of exposure, confirmed by biometrics, still suggested a higher risk in satralizumab-mwge treatment.

Interruptions and Discontinuations

Study 307JG

Four patients (9.5%) treated with placebo and 3 patients (7.3%) treated with satralizumab-mwge who were anti-AQP4 antibody positive discontinued treatment in Study 307JG because of adverse events. The reasons for these three discontinuations of satralizumab-mwge treatment were increased liver transaminases, low neutrophil count, and urticaria, all which have been described as side effects of other anti-IL6 receptor monoclonal antibody therapies. Labeling will describe risks of increased transaminase and neutropenia associated with treatment, and we are requesting enhanced pharmacovigilance for hepatotoxicity. These adverse events are known to occur with other biologics that target the IL-6 receptor. The description of the discontinuation event characterized by urticaria with diffuse pruritis worsening with repeated doses is potentially consistent with a systemic hypersensitivity reaction to satralizumab-mwge and justifies a labeling warning of a risk of hypersensitivity.

Study 309JG

A patient discontinued placebo treatment due to systemic lupus erythematosus and a patient who was anti-AQP4 antibody negative discontinued satralizumab-mwge treatment because of pneumonia.

Treatment-Emergent Adverse Events

Study 307JG

The following table summarizes the most common adverse events that occurred in the controlled phase of Study 307JG:

Table 10: Treatment Emergent Adverse Events During Controlled Phase of Study 307JG Occurring in 2 or More of Satralizumab-mwge-treated Patients and Greater Than Placebo, Safety Population

Adverse Event Preferred Term	Placebo (N=42)	Satralizumab-mwge (N=41)
Headache	4 (9.5%)	10 (24.4%)
Upper respiratory tract infection	6 (14.3%)	10 (24.4%)
Nasopharyngitis	7 (16.7%)	10 (24.4%)
Urinary tract infection	7 (16.7%)	7 (17.1%)
Leukopenia	3 (7.1%)	6 (14.6%)
Hypercholesterolemia	5 (11.9%)	4 (9.8%)
Gastritis	0 (0.0%)	4 (9.8%)
Back pain	5 (11.9%)	4 (9.8%)
Arthralgia	0 (0.0%)	4 (9.8%)
Pharyngitis	3 (7.1%)	4 (9.8%)
Nausea	3 (7.1%)	3 (7.3%)
Cystitis	4 (9.5%)	3 (7.3%)
Urticaria	0 (0.0%)	3 (7.3%)
Rhinitis	0 (0.0%)	3 (7.3%)
Sinusitis	0 (0.0%)	3 (7.3%)
Anemia	5 (11.9%)	3 (7.3%)
Oropharyngeal pain	1 (2.4%)	3 (7.3%)
Lymphopenia	4 (9.5%)	3 (7.3%)
Hypertension	0 (0.0%)	3 (7.3%)

Source: Clinical Review, Table 84

As the previous table demonstrates, most of the adverse events occurring relatively more often in association with satralizumab-mwge (e.g., headache, upper respiratory

tract infection, nasopharyngitis) are treatable and are not usually life-threatening. Although other anti-IL-6 receptor antagonists are associated with neutropenia, the increased risk of lymphopenia/leukopenia is difficult to interpret as a risk specific to satralizumab-mwge because Study 307JG allowed concurrent use of azathioprine and mycophenolate mofetil, which also can induce lymphopenia. There are also pain-related adverse events represented at high frequencies in both treatment conditions, confirming that pain is a significant chronic issue for all patients with NMOSD. An analysis limited only to anti-AQP4 antibody positive patients revealed only greater risks of nasopharyngitis, headache, upper respiratory tract infection, gastritis, arthralgia, and pharyngitis as events occurring at higher frequencies in satralizumab-mwge treatment. Increased risk of infections is expected in immune suppression and will be a labeled risk. Gastritis is a notable finding because other anti-IL-6 receptor antagonists have been associated with a risk of gastrointestinal perforation, hence the study protocols for Studies 307JG and 309JG stipulated a need to conduct upper gastrointestinal endoscopies routinely on all patients in the trial. However, there were no cases of perforation in these studies, and the gastritis reported in these studies was consistent with gastroesophageal reflux disease that is idiopathic (and common in the general population) or was consistent with corticosteroid use in patients on concurrent steroid therapy. (b) (4) is therefore not justified by the findings in these trials and appears unique to the indicated systemic autoimmune conditions these other anti-IL-6 receptor antagonists are approved to treat. Increased risk of pain is discussed in Study 309JG's results.

Injection-related reactions occurred much more often in the satralizumab-mwge treatment condition (12.2%) than in the placebo condition (4.8%). The most common local reactions were swelling and redness; the most common systemic symptoms were headache and flushing. There were no serious or fatal injection-related reactions in Study 307JG suggesting that administration of satralizumab-mwge is relatively well-tolerated and appears safe for patients to do themselves outside of a medically monitored setting.

Dr. Rodichok reviewed all treatment-emergent adverse events in just anti-AQP4 antibody positive patients and noted there were no obvious safety signals uniquely represented in that majority subset of the trial's patients. Labeling will only refer to safety findings in anti-AQP4 antibody positive patients.

Study 309JG

The following table summarizes the most common adverse events that occurred in the controlled phase of Study 309JG:

Table 11: Treatment Emergent Adverse Events During Controlled Phase of Study 309JG Occurring in 3 or More of Satralizumab-mwge-treated Patients and Greater Than Placebo, Safety Population

Adverse Event Preferred Term	Placebo (N=32)	Satralizumab-mwge (N=63)
Urinary tract infection	8 (25.0%)	11 (17.5%)
Nausea	2 (6.3%)	11 (17.5%)
Upper respiratory tract infection	6 (18.8%)	10 (15.9%)
Headache	4 (12.5%)	10 (15.9%)
Arthralgia	1 (3.1%)	10 (15.9%)
Nasopharyngitis	1 (3.1%)	9 (14.3%)
Rash	1 (3.1%)	9 (14.3%)
Pain in extremity	3 (9.4%)	9 (14.3%)
Pruritus	0 (0.0%)	7 (11.1%)
Fatigue	2 (6.3%)	7 (11.1%)
Depression	1 (3.1%)	6 (9.5%)
Hypoesthesia	0 (0.0%)	5 (7.9%)
Influenza	2 (6.3%)	5 (7.9%)
Insomnia	1 (3.1%)	5 (7.9%)
Diarrhea	0 (0.0%)	5 (7.9%)
White blood cell count decreased	0 (0.0%)	5 (7.9%)
Migraine	0 (0.0%)	4 (6.3%)
Cellulitis	0 (0.0%)	4 (6.3%)
Neutropenia	1 (3.1%)	4 (6.3%)
Edema peripheral	0 (0.0%)	4 (6.3%)
Musculoskeletal stiffness	0 (0.0%)	4 (6.3%)
Alanine aminotransferase increased	0 (0.0%)	4 (6.3%)
Myalgia	0 (0.0%)	4 (6.3%)
Blood creatine phosphokinase increased	1 (3.1%)	4 (6.3%)
Musculoskeletal pain	2 (6.3%)	4 (6.3%)
Back pain	3 (9.4%)	4 (6.3%)
Fall	2 (6.3%)	4 (6.3%)

Source: Clinical Review, Table 78

As indicated in the table, the most frequently reported treatment-emergent adverse events in Study 309JG were almost identical (e.g., headache, upper respiratory tract infection, nasopharyngitis) to the most common risks associated with satralizumab-

mwge treatment in Study 307JG. As mentioned, increased risk of infections will be a labeled warning for Enspryng. Since Study 309JG did not allow patients to continue baseline immunosuppressants, the continued observation of neutropenia/low white blood cell count in this study appears to be a true treatment-emergent effect of this specific therapy which aligns with safety findings in other anti-IL-6 receptor antagonists. Neutropenia should be a labeled warning for Enspryng. Increased risks of pain in extremities, arthraligia, and myalgia are noted in this study and also were noted in placebo-controlled trials of Soliris and Uplizna for the treatment of NMOSD. There was an indication of a trend towards increased pain reported after 24 weeks of treatment with satralizumab-mwge as measured by the VAS pain assessment in these two studies noted by the clinical and biometrics reviewers. The origin of this consistent finding of an increase in pain phenomena is unclear but with these same risks occurring in well-controlled trials using three therapies with completely different mechanisms; this is not unique to satralizumab-mwge.

In Study 309JG, injection-related reactions occurred more often in the placebo condition (15.6%) than in the satralizumab-mwge treatment condition (12.7%). The most common local reactions associated with satralizumab-mwge were pain, swelling, and erythema. Dr. Rodichok notes that the applicant's pre-specified list of injection reactions included many preferred terms for adverse events which are not typically considered to be injection-related. For example, the most common systemic symptom in Study 309JG was loose stools/diarrhea, which occurred in two patients soon after administration of satralizumab-mwge, and which, in Dr. Rodichok' s opinion, did not seem plausibly linked to treatment. There was a single moderate reaction not requiring hospitalization, and, as was the case in Study 307JG, there were no severe or fatal injection-related reactions in Study 309JG. Administration of satralizumab-mwge is relatively well-tolerated and appears safe for patients to self-administer. There does not appear to be a need for premedication because the most common reactions were relatively mild, and patients did not discontinue satralizumab-mwge because of them. Because the other monoclonal antibody IL-6 receptor antagonists have been associated with anaphylaxis, I agree with Dr. Rodichok that given the relatively limited experience with satralizumab-mwge, even in the absence of an observed severe true anaphylactic reaction, a risk for severe reactions exists. The labeling for Enspryng should include a potential risk of serious reactions including anaphylaxis.

Dr. Rodichok reviewed all treatment-emergent adverse events in just anti-AQP4 antibody positive patients in Study 309JG and noted no obvious safety signals uniquely represented in that majority subset of the trial's patients. Labeling will only refer to safety findings in anti-AQP4 antibody positive patients.

Adverse Events of Special Interest and Special Safety Concerns

Dr. Rodichok's review identified several submission-specific safety issues as follows: risks of serious infections, neutropenia, and injection-related reactions. The risks of neutropenia and injection-related reactions, and proposed mitigations, have been discussed above.

Serious Infections
The findings from Study 307JG did not show a clearly higher rate of SAEs but did demonstrate more serious infections, but this was confounded by the allowed use of other immunosuppressants. In Study 309JG, there was a noted higher risk of SAEs in patients treated with satralizumab-mwge; the SAEs included influenza, urosepsis, pyelonephritis, pneumonia, and sepsis. The findings in Study 309JG are not confounded by other immunosuppressants. Treatment-emergent infections noted in Study 309JG were more frequent in the satralizumab-mwge treated group. Dr. Rodichok expresses concerns that the safety database from these two trials is relatively small and may not reflect the postmarketing setting especially for serious infections. Therefore, labeling should include a description of the possible risk of serious infections, a contraindication to initiating treatment in patients with active infection, and a consideration for pausing treatment in patients with serious infections. The labeling for other anti-IL-6 receptor therapies has a boxed warning for serious infection risks which further justifies this approach, but a boxed warning for Enspryng is not needed because there were no life-threatening or fatal infections in these studies. Enhanced pharmacovigilance will be requested to ensure that serious or opportunistic infections are reported promptly and to allow prompt labeling changes in response to emerging safety signals.

The approved monoclonal antibodies that antagonize the IL-6 receptor, Actemra and Kevzara, have a boxed warning citing a specific risk of reactivated latent tuberculosis. Studies 307JG and 309JG screened for tuberculosis infection in patients and excluded patients with latent tuberculosis. Therefore, the absence of tuberculosis infections in these trials is the result of screening and is not reassuring of an absence of risk. There is a literature supporting the hypothesis that inhibition of IL-6 receptors promotes tuberculosis infection and reactivation. There is no evident reason based on the understand of its mechanism of action why satralizumab-mwge would not confer a similar risk of potentially serious or fatal tuberculosis infections. Therefore, to ensure safe use of Enspryng, labeling will contraindicate the use of Enspryng in patients with active or untreated latent tuberculosis and indicate that screening for tuberculosis is required prior to initiating therapy. Similarly, the labeling for Actemra and Kevzara

indicate that immune suppression can exacerbate hepatitis B infection, but, as with tuberculosis, patients with hepatitis B infection were excluded from these studies. IL-6 signaling via IL-6 receptors in the liver plays a complex role in hepatitis B infection, and it is not clear that therapies like Enspryng can be used safely in the setting of hepatitis B infection. Therefore, the use of Enspryng in patients with active hepatitis B infection will be contraindicated and labeling will indicate that screening for hepatitis B should be performed before use of Enspryng.

Pediatric Patients

Study 307JG included seven patients below the age of 18 years old. Four of these patients were exposed to at least one dose of satralizumab-mwge; all these patients were on concurrent immune suppressing therapies. The small number of patients, few events, and confounding effects of other immunosuppressive treatments did not allow for any conclusions regarding the safety of satralizumab-mwge in patients less than 18 years old.

Safety Conclusions

Satralizumab-mwge is associated with several adverse reactions, some of which are serious, most prominently risks of serious infections, neutropenia, and injection-related reactions. However, these risks can be adequately described in labeling with the potential for many to be reduced or managed with screening and appropriate intervention (including discontinuation of therapy). Some of the most common adverse events related to pain were noted in another NMOSD development program and raise the possibility of a non-specific risk of unclear significance and etiology. Otherwise, the identified risks are consistent in frequency and type with other approved therapies that block IL-6 binding to the IL-6 receptor used in other serious indications such as rheumatoid arthritis and temporal arteritis. The safety profile of satralizumab-mwge supports approval for the treatment of NMOSD, a serious, potentially fatal, disease. There will be expedited reporting of serious infections through enhanced pharmacovigilance. A postmarketing required study to evaluate pregnancy exposures and potential effects on offspring exposed in utero is needed to provide additional data to inform the safety of satralizumab-mwge in this vulnerable population.

9. Advisory Committee Meeting

This application was not referred to an advisory committee for review because the safety profile is similar to that of other biologics with similar mechanisms that are approved for other indications, the clinical trial designs were acceptable, the efficacy findings were clear, and the safety profile was acceptable in light of the serious nature

of the disease being treated. Labeling will make prescribers aware of the risks associated with satralizumab-mwge treatment.

10. Pediatrics

NMOSD is rare in children and adolescents. In addition, this development program has orphan drug designation, and so the Pediatric Research Equity Act is not triggered. Study 307JG included seven patients less than 18 years old but the findings in this subpopulation did not support conclusions regarding efficacy and safety.

11. Other Relevant Regulatory Issues

- The review of this application did not identify any Good Clinical Practice (GCP) issues.
- Dr. Rodichok concluded that the applicant has adequately disclosed financial interests and arrangements with the clinical investigators.
- The Controlled Substance Staff (CSS) provided a consultation. The CSS review reaffirmed their prior review of IND 118183 that satralizumab-mwge did not demonstrate potential for abuse.
- The Division of Risk Management (DRM) did not recommend a REMS for satralizumab-mwge.
- The Office of Scientific Investigations (OSI) completed inspections of two investigators' sites (Drs. Eubank and Javed). Their inspection of Dr. Eubank's site identified a patient included in the primary efficacy analysis who had withdrawn consent for Study 307JG one month prior to experiencing a relapse. A sensitivity analysis removing this patient from the primary analysis did not significantly alter the primary efficacy outcome. (b) (4)

(b) (4)

(b) (4)

12. Labeling

Please refer to the final negotiated product label.

13. Postmarketing Recommendations

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The following is a postmarketing requirement:

- Establish a worldwide single-arm pregnancy safety study to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to Enspryng (satralizumab-mwge) during pregnancy in patients with neuromyelitis optica spectrum disorder (NMOSD). Provide a complete protocol that includes details regarding how you plan to encourage patients and providers to report pregnancy exposures, measures to ensure complete data capture regarding pregnancy outcomes and any adverse effects in offspring, and plans for comprehensive data analysis.

Draft Protocol Submission:	04/2021
Final Protocol Submission:	12/2021
Annual Interim Report Submissions:	12/2022
	12/2023
	12/2024
	12/2025
	12/2026
	12/2027
	12/2028
	12/2029
	12/2030
	12/2031
Study Completion:	12/2032
Final Report Submission:	12/2033

14. Recommended Comments to the Applicant

There are no additional recommended comments to the applicant. The approval letter will request enhanced pharmacovigilance for serious and opportunistic infections including fatal infections, thrombocytopenia, and hepatotoxicity.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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08/14/2020 05:47:41 PM

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