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APPLICATION NUMBER:

761142Orig1s000

SUMMARY REVIEW

Summary Review

Date	June 11, 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 #	761142
Applicant	Viela Bio
Date of Submission	June 11, 2019
PDUFA Goal Date	June 11, 2020
Proprietary Name	Uplizna
Established or Proper Name	Inebilizumab-cdon
Dosage Form(s)	Intravenous
Applicant Proposed Indication(s)/Population(s)	Adults with neuromyelitis optica spectrum disorders (NMOSD)
Applicant Proposed Dosing Regimen(s)	Initial 300 mg intravenous infusion followed two weeks later by a second 300 mg intravenous infusion, and a single 300 mg intravenous infusion every 6 months thereafter, starting 6 months from the first infusion
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)	Initial 300 mg intravenous infusion followed two weeks later by a second 300 mg intravenous infusion, and a single 300 mg intravenous infusion every 6 months thereafter, starting 6 months from the first infusion

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.

The average age of onset of NMOSD is approximately forty 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 ratio of men to women with NMOSD is greater than 2:1. 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 heterogenous population whose natural history and treatment response differs from those of patients with anti-AQP4 antibodies.

Uplizna (inebilizumab-cdon) is a humanized, afucosylated IgG1 kappa monoclonal antibody that binds to the CD19 surface antigen on B-cells, including B-cell precursors and some B-cells that secrete antibodies. When inebilizumab-cdon binds to a B-cell expressing CD19 surface antigen, the inebilizumab-cdon-bound cell is targeted subsequently for antibody-mediated cellular phagocytosis. Therefore, inebilizumab-cdon preferentially targets B-cells for destruction and yields a significant, sustained reduction in circulating serum B-cell numbers. By reducing B-cells that express CD19, inebilizumab-cdon is intended to lower the likelihood of relapses associated by interfering with the autoimmune processes that are presumed to occur in NMOSD.

The applicant provides data from Study MEDI-551-1155 ("Study 1155" in this memorandum), a prospective, double-blind, placebo-controlled, randomized

trial. The trial evaluated a 300 mg dose of inebilizumab-cdon (or placebo infusion) given intravenously once on Day 1, and a second dose on Day 15, followed by single 300 mg doses every six months. The trial randomized 231 patients in a 3:1 ratio to treatment with inebilizumab-cdon or placebo. There were 175 patients with NMOSD randomized to inebilizumab-cdon treatment and 56 patients randomized to placebo treatment. Enrollment required that patients met the 2006 international criteria for NMOSD. Most (over 90%) of the randomized patients were positive for anti-AQP4 antibodies; there were 17 patients who were negative for anti-AQP4 antibodies. The primary outcome efficacy measure of this trial was the time from Day 1 of trial randomization to the onset of a protocol-defined, adjudicated NMOSD relapse or to the end of the randomized controlled phase of the trial. All reported relapses were subject to review by an independent adjudication committee, and only adjudicated relapses were considered as the primary endpoint in the statistical analysis.

In Study 1155, patients with NMOSD who were positive for anti-AQP4 antibodies in the inebilizumab-cdon treatment arm experienced a highly statistically significant ($p<0.0001$) treatment effect manifesting as a 77% relative reduction in adjudicated relapses compared to patients treated with placebo. There was no effect of treatment in patients with NMOSD who were negative for anti-AQP4 antibodies. Secondary outcome measures demonstrated significant reductions in new central nervous system lesions and in annual hospitalization rates in the anti-AQP4 seropositive patients.

The safety findings in Study 1155 showed that inebilizumab-cdon was generally well-tolerated. Patients treated with inebilizumab-cdon appeared to experience a reduction in adverse events associated with NMOSD relapses. The adverse events associated with inebilizumab-cdon included the expected risks associated with B-cell depletion such as higher rates of some infections and declining serum immunoglobulin levels. The two deaths in the NMOSD development program were not clearly related to inebilizumab-cdon. The short duration of the trial exposure precluded definitive resolution of a concern that declining serum immunoglobulin levels could yield clinically significant hypogammaglobulinemia; labeling warnings with recommended screening and a postmarketing study will clarify the potential risks of hypogammaglobulinemia associated with treatment. A required postmarketing pregnancy observation trial will examine outcomes from fetal exposure because animal data suggest inebilizumab-cdon exposure may alter the immune system of offspring. No safety issues were identified that would require a risk evaluation and mitigation strategy (REMS).

Study 1155 provided significant, clear, and robust efficacy findings of inebilizumab-cdon for the treatment of NMOSD in adult patients who are anti-AQP4 antibody positive, a serious, disabling, and possibly fatal disease with only one approved therapy. Given the strength of the study's findings on an accepted clinical outcome measure in these patients, time to relapse, as well as the support from a number of conservative sensitivity analyses and the analyses of important secondary endpoints (e.g., reduction in hospitalizations), the evidence of effectiveness presented in in the application is persuasive and reliance on a single clinical trial to support approval is justified. The most common potentially serious safety risk of inebilizumab-cdon, increased risk of infections, can be addressed through labeling and does not preclude approval of this highly 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.
	• 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%) 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.
Current Treatment Options	• Soliris (eculizumab), a monoclonal antibody targeting C5, is the only approved treatment for NMOSD in adult patients who are anti-AQP4 antibody positive.	Soliris is the only approved treatment 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.	
Benefit	• The applicant provides data from a 3:1 randomized, double-blind, placebo-controlled time to event trial in 231 adult patients with NMOSD with and without anti-AQP4 antibodies treated with inebilizumab-cdon or placebo in which the primary outcome efficacy measure was the time to first relapse on trial.	The data from the clinical trial provided in this application establish the effectiveness of inebilizumab-cdon for the treatment of NMOSD in adult patients who are anti-AQP4 antibody positive.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Treatment with inebilizumab-cdon reduced the relative risk of a relapse in patients with anti-AQP4 antibodies by 77% relative to placebo treatment ($p<0.0001$). • Patients who were anti-AQP4 antibody positive who were treated with inebilizumab-cdon also had reduced estimated annualized inpatient hospitalization rates relative to placebo-treated patients. • Treatment with inebilizumab-cdon did not have a significant effect on the relative risk of relapse in patients who were anti-AQP4 antibody negative compared to placebo treatment.	The reduced relapse frequency for anti-AQP4 antibody positive patients is highly statistically significant and supported by multiple sensitivity analyses, as well as analyses of clinically meaningful secondary endpoints (e.g., reduced hospitalizations). Relapses are significant clinical events that can cause permanent disability. Preventing and reducing the frequency of relapses is a meaningful clinical outcome for patients with NMOSD. There was no evidence of a clinical benefit for anti-AQP4 antibody negative patients.
Risk and Risk Management	• Overall, patients treated with inebilizumab-cdon in a placebo-controlled blinded clinical trial had comparable risks of most adverse events and experienced fewer serious adverse events than patients treated with placebo. • There were two deaths of patients treated with inebilizumab-cdon that occurred after the randomized controlled trial period. One of these cases involved a 68-year-old woman who died from the sequelae of a new lesion which was consistent with, but not definitively confirmed as, an opportunistic infection such as progressive multifocal leukoencephalopathy (PML). • The most common risks of treatment with inebilizumab-cdon appear to be an increased risk of urinary tract infections and pain. Patients treated with inebilizumab-cdon appeared to have an approximately 2% higher risk of urinary tract infection and nearly 3% higher rate of cystitis compared with placebo-treated patients. Joint pain (7%), back pain (4%), paresthesia (3%), and eye pain (1%) occurred at a relatively higher rate as indicated in patients treated with inebilizumab-cdon as compared to placebo treatment.	Despite causing a reduction in B-cells, treatment with inebilizumab-cdon did not appear to confer a greater risk of most infections than placebo treatment. The risks identified with inebilizumab-cdon therapy appear manageable with labeling and monitoring. NMOSD is a serious, potentially fatal condition. The two deaths that occurred in the development program for inebilizumab-cdon were not clearly directly attributable to therapy. Though the death due to a brain lesion was not definitively proven to be due to PML, labeling will describe the presence of active infection as a contraindication of treatment and state that serious infections due to inebilizumab-cdon treatment, such as PML, may occur. Urinary tract infections and pain are manageable

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Lymphopenia, neutropenia, and reduced serum immunoglobulins only occurred in patients treated with inebilizumab-cdon. Diminished immunoglobulin levels were persistent throughout the clinical trial and continued to trend downward with increased treatment duration during the open-label extension without reaching a clear nadir. • Studies in animals suggested there is depletion of B-cells and diminished immune system reactivity to novel antigens in exposed offspring.	conditions. A higher reported rate of joint and back pain has been noted in a trial of another NMOSD therapy and does not appear to be a treatment-specific finding for inebilizumab-cdon. Hepatitis B infection can reactivate in patients treated with therapies with mechanisms of action similar to inebilizumab-cdon, and so a warning regarding adequate assessment of hepatitis B will be included in labeling. The clinical trial specifically excluded patients with a history of tuberculosis (TB), and so a warning for adequate treatment of patients with prior history of TB will be included, as well. A postmarketing requirement will be imposed for an investigation to monitor immunoglobulin levels in patients receiving chronic inebilizumab-cdon therapy with a goal of identifying if there is a nadir to immunoglobulin reductions observed in the clinical trial. This trial will monitor B-cell counts and the risks of serious and opportunistic infections. This trial will also observe patients who discontinue therapy to determine the timeline for restoration of normal circulating levels of immunoglobulins. A postmarketing pregnancy surveillance study will also be required.

2. Background

This original biologics license application (BLA) contains data in support of the efficacy and safety of inebilizumab-cdon, administered as an intravenous (IV) injection, for the proposed treatment of adult 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 half of patients diagnosed with NMOSD will have a detectable titer of anti-AQP4 antibodies in their serum or spinal fluid.

Inebilizumab-cdon is a humanized, afucosylated IgG1 kappa monoclonal antibody that binds to the CD19 surface antigen on B-cells, including plasma blasts and plasma cells that secrete antibodies. The reduction in B-lymphocytes associated with inebilizumab-cdon administration is mediated by antibody-dependent cellular cytotoxicity (ADCC) and by antibody-dependent cellular phagocytosis (ADCP) of targeted lymphocytes.

There is one approved treatment for NMOSD, Soliris (eculizumab), which 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.

This application contains data from Study CD-IA-MEDI-551-1155 (Study 1155), a prospective, randomized, placebo-controlled trial as the primary basis of support for the safety and effectiveness of inebilizumab-cdon in the treatment of NMOSD. Additional safety information comes from the open-label extension (OLE) phase of Study 1155, CD-IA-MEDI-551-1155 OLE.

Dr. Lawrence Rodichok's clinical review provides the regulatory history of the development program for inebilizumab-cdon for the treatment of NMOSD. This development program was granted orphan drug designation for the treatment of NMOSD on February 10, 2016, and was granted breakthrough therapy designation for the treatment of NMOSD on March 17, 2019 (prior to the approval of Soliris). Currently, inebilizumab-cdon is not approved for the treatment of any indication in the United States or elsewhere.

3. Product Quality

The Office of Biotechnology Products (OBP) provided a review of product quality. Dr. Li Lu was the primary reviewer, Dr. Bazarragchaa Damdinsuren was the application technical lead, and Dr. Christopher Downey was the review chief. 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 inebilizumab-cdon 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, and the product had been consistently manufactured from multiple production runs. The review confirmed the applicant's stability assertions. The review agreed with the applicant's proposed shelf-life of 36 months when stored at 2-8°C for the drug product. The OBP review also agreed that a shelf-life of (b) (4) months when stored at (b) (4) was appropriate for the drug substance.

The review team found that the applicant's immunogenicity assay to detect anti-drug antibodies in patient serum samples was appropriately validated and capable of evaluating non-neutralizing anti-drug antibodies accurately. However, the review noted that the

applicant presently does not have an assay capable of detecting neutralizing antibodies. In a meeting with the applicant in June 2016, the Agency had agreed with the applicant's plan regarding options for an indirect assessment of neutralizing antibodies without a neutralizing antibody assay. The review team was aware of the absence of a neutralizing antibody assay in this application and concluded a neutralizing assay was not necessary for approval because, as previously agreed, the applicant had supplied adequate evidence of maintained efficacy and safety of inebilizumab-cdon despite the presence of anti-drug antibodies, some of which, presumably, could have been neutralizing.

The OBP review team found that the manufacturing facilities for the drug substance and drug product were both acceptable based on their currently acceptable Current Good Manufacturing Practice (CGMP) compliance status.

The OBP team requests a postmarketing commitment for a study to confirm the stability of the drug substance during shipping under conditions through a route from its manufacturing facility for the drug substance (b) (4) to its facility for manufacturing the drug product (b) (4)

Dr. Candace Gomez-Broughton provided the primary Division of Microbiology Assessment review, and Dr. Reyes Candau-Chacon provided a supervisory review. Dr. Gomez-Broughton recommends approval; Dr. Candau-Chacon endorses approval. The microbiology review did not identify any significant issues in the manufacturing and shipping of inebilizumab-cdon from a sterility assurance perspective.

Dr. Aimee Cunningham provided a Product Quality Microbiology review. The team lead was Dr. Reyes Candau-Chacon. Dr. Cunningham concluded that the drug substance portion of the BLA submission had no significant microbial control or product quality issues from a microbiology standpoint. The Product Quality Microbiology review team recommends approval.

4. Nonclinical Pharmacology/Toxicology

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

- An adequate battery of pharmacology studies was conducted to characterize the specificity, affinity, and mechanism of action of inebilizumab-cdon. By prior agreement with the Agency, there were no carcinogenicity nor mutagenicity studies conducted. The data confirm that this product binds to human CD19 (huCD19) with high affinity and specificity and does not bind to CD19 of other species. Therefore, toxicology studies were conducted using a transgenic mouse model expressing huCD19.

- In vitro studies demonstrated that inebilizumab-cdon binding results in rapid depletion of B-lymphocyte populations through the processes of ADCC and, to a lesser degree, ADCP. The observed depletion is dose-related in magnitude and duration and does not significantly impact other immune cell populations.

- In all nonclinical toxicology studies, dose-related depletion of CD19-expressing B-lymphocytes in peripheral blood, bone marrow, and lymphoid tissues (spleen and lymph nodes) was observed. Duration of the effect was dose-dependent, but full recovery was documented if sufficient recovery time was provided. At the highest dose tested, full recovery required up to 36 weeks. There were skin lesions observed in 3-month and 6-month studies consistent with immunosuppression.

- Dose-related effects were observed in a combined fertility and early embryofetal development study conducted in a mouse expressing huCD19. Mice that received 0, 3, or 30 mg/kg doses of inebilizumab-cdon weekly beginning 15 days prior to mating and through gestational day 15 showed reduced fertility index at both dose levels. The reduced number of pregnancies in mice that had successfully mated appeared to be due to early preimplantation loss. No adverse effects were observed on embryofetal development.

- Dose-related effects were also observed in a pre-and postnatal development study in which pregnant mice received IV doses of inebilizumab-cdon every 3 days from gestational day 6 through weaning of the offspring. Offspring from the low-dose and high-dose groups showed a near total absence of B-cells. At the end of the study, with no further exposure to inebilizumab-cdon, B-cell levels in offspring from the low-dose and high-dose groups were similar to controls. However, in functional immune testing conducted when the offspring had matured, the offspring from both the high- and low-dose groups showed impaired responses to immunization. These data indicate that, although at normal levels, the offspring's lymphocytes did not function normally to mount an appropriate immune response to vaccinations. The finding of B-cell depletion in offspring and reduced immunization response in offspring will be described in labeling as warnings regarding the potential adverse effects of in utero exposure.

- 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, inebilizumab-cdon 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 and Michael Bewernitz were primary reviewers, and Drs. Atul Bhattaram and Angela Men were team leads. Dr. Mehul Mehta was the Division Director. The OCP team recommends approval.

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

Table 1: General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Inebilizumab-cdon is a humanized IgG1 monoclonal antibody targeting CD19+ B cells. By binding to B-cells (also known as B lymphocytes), inebilizumab-cdon mediates ADCC and ADCP.
QT Prolongation	No formal QT evaluation has been conducted for inebilizumab-cdon. As a large molecule, inebilizumab-cdon has a low likelihood to directly interact with ion channels.
General Information	
Bioanalysis	Inebilizumab-cdon was measured using validated Enzyme Linked Immunosorbent Assay (ELISA) methods.
Drug Total Exposure Following the Therapeutic Dosing Regimen	The mean maximum concentration was 108 μg/mL, and the cumulative AUC of the 26-week treatment period was 2980 μg·d/mL following two IV administrations (300 mg, 2 weeks apart).
Dose Proportionality	The systemic exposures increased approximately proportionally with an increase in dose from 30 mg to 600 mg.
Immunogenicity	In Study 1155, the incidence of treatment-emergent anti-drug antibody incidence in patients treated with inebilizumab-cdon at any timepoint was 5.6% (12 of 213 exposed patients). The presence of anti-drug antibodies did not appear to have a clinically-relevant impact on PK parameters, pharmacodynamic

	(PD) parameters, or the efficacy and safety of inebilizumab-cdon.
Inhibitor/Inducer Potential	Not evaluated. As a large recombinant protein, inebilizumab-cdon is not expected to be an inhibitor or inducer of drug metabolism enzymes or transporters.
Distribution	
Volume of Distribution	Central and peripheral volume of distribution was 2.95 L and 2.57 L, respectively.
Elimination	
Terminal Elimination Half-life	Approximately 18 days.
Metabolism / Excretion	As a humanized IgG1 monoclonal antibody, inebilizumab-cdon is degraded into small peptides and amino acids by proteolytic enzymes widely distributed in the body.

All patients with NMOSD in Study 1155 who received inebilizumab-cdon had significant, sustained reductions in serum CD19+ B-lymphocytes. However, the OCP review noted that while Study 1155 provided evidence of a reduction in relapses in patients treated with inebilizumab-cdon who were anti-AQP4 antibody positive (see Section 7 of this review), the study failed to provide adequate evidence of clinical effectiveness in the patients who were anti-AQP4 antibody negative despite an identical reduction in lymphocytes. As a result of this discrepancy in clinical outcomes between NMOSD patients who were anti-AQP4 antibody positive and negative, and the absence of a clear PK exposure relationship to efficacy outcomes, an exposure-response analysis could not provide any additional evidence to support efficacy for all patients with NMOSD.

The OCP review concluded that inebilizumab-cdon clearance is likely similar to endogenous immunoglobulin clearance via the reticuloendothelial system and that the risk of inebilizumab-cdon interaction with other therapies is low.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Larry Rodichok was the clinical reviewer for this application. Dr. Xiangmin Zhang was the biometrics reviewer, Dr. Kun Jin was the team lead, and Dr. Hsien Ming Hung was the biometrics Division Director for this application.

Study 1155

The applicant submitted findings from a single adequate and well-controlled efficacy trial in support of this application. Study 1155 was a 230-patient, randomized, double-blind, placebo-controlled, multicenter trial. Patients enrolled in Study 1155 were not permitted to be concurrently using any other immunosuppressant therapies (e.g., corticosteroids, rituximab) commonly prescribed off-label to treat NMOSD (Soliris was unapproved at the time that Study 1155 was conducted).

Inclusion criteria for Study 1155 were based on clinical criteria for "neuromyelitis optica" (NMO) as defined in publications by Wingerchuk in 2006 and revised in 2007. These criteria underwent significant revision in 2015 after this trial began enrollment, and, among other changes, NMO was renamed "NMOSD." The study's enrollment criteria did not change to avoid the potential of having two different enrolled populations; however, the enrolled patients also met the new accepted criteria for a diagnosis of NMOSD, and thus this trial's population remained representative of patients with the contemporary diagnosis of NMOSD.

In the most recent revision to the diagnostic criteria, anti-AQP4 antibody status was no longer a major criterion for a diagnosis of NMOSD (anti-AQP4 antibody status is now an additional disease descriptor). However, Study 1155 had sought to enroll and to stratify patients with and without anti-AQP4 antibodies in a ratio of 9:1 to approximate the reported frequency of the presence of anti-AQP4 antibodies in the NMOSD population using the original criteria.

The protocol stipulated a screening period of up to 28 days after which eligible patients entered the randomized controlled phase and were dosed in a 3:1 ratio with either IV inebilizumab-cdon 300 mg on Day 1 and on Day 15, or matching placebo. Patients were stratified by anti-AQP4 antibody status at screening, then further stratified by region (i.e., Japan versus non-Japan). Patients were followed for a period of 197 days, and patients exited the randomized trial phase when they experienced an independently-verified relapse or reached the 197th study day without a verified relapse. These patients were then invited to enter an open-label extension trial to receive inebilizumab-cdon for up to three years.

An adjudication committee (AC) provided independent verification of relapses for patients in the controlled trial phase. Enrollment of patients was planned to end when a total of 67 AC-confirmed relapses had occurred in the randomized phase of the trial, or when 252 patients had been randomized and dosed, or following any recommendation by the Independent Data Monitoring Committee (IDMC) to stop the trial. On September 7, 2018, the IDMC recommended stopping the trial after reviewing the trial's interim unblinded

findings reasoning it was not ethical to continue to expose patients to a higher relapse rate in the placebo arm given the efficacy findings in the active treatment arm. At the time of the trial's end, 43 AC-confirmed relapses had occurred; the trial had enrolled 231 patients with 230 of them having been treated.

The primary efficacy endpoint for Study 1155 was the time, in days, from Day 1 of the trial to the date of the first AC-confirmed relapse or to Day 197 (i.e., 197 days) if no AC-confirmed relapses occurred. When a patient presented with a potential relapse, after a blinded evaluation at a clinical site, the AC received a full set of clinical and radiologic records regarding the event. The AC adjudicated a possible relapse (termed an "attack" in the protocol) using a systematic procedure and relied on a pre-specified set of 18 criteria that defined a relapse event within 3 bodily domains (optic nerve, spinal cord, and brain/brainstem). The data provided to the AC was blinded and did not include treatment assignment or laboratory values that could identify treatment assignment such as B-cell counts.

Results

Demographics
The intention-to-treat (ITT) population comprised 230 patients total, 213 patients of whom were seropositive for anti-AQP4 antibodies, and 17 who were seronegative for anti-AQP4 antibodies. A patient was randomized to inebilizumab-cdon treatment but was not treated and therefore excluded from the ITT population analyzed by the applicant.

The applicant's ITT population was consistent with the reported demographics of NMOSD. More than 90% of the randomized patients were women, approximately 60% were at least 40 years old, and over 70% were White or Asian. There were no apparent demographic differences between the anti-AQP4 seropositive and seronegative populations.

Primary Outcome Measure
There were 64 possible relapse events adjudicated by the AC, 36 in the group treated with inebilizumab-cdon (20.7% of the treatment group) and 28 in the placebo group (50% of the treatment group). Twenty-one of the 36 (58.3%) events in the inebilizumab-cdon group were confirmed by the AC; 22 of the 28 (79%) in the placebo group were confirmed by the AC. Dr. Rodichok noted a concern that the 20% higher rate of AC-confirmed relapses in the placebo treatment group could be indicative of bias towards the active treatment group. A review of the materials presented to the AC for adjudication did not reveal any sources of unblinding. The Expanded Disability Status Scale (EDSS) score changes in AC-confirmed relapses were a point higher than patients' baseline measurements (a clinically meaningful change). There were no differences in the EDSS changes, in the location of relapses, nor in the criteria used to confirm relapses between the active and placebo treatment arms. It is noteworthy that a higher adjudication confirmation rate in the placebo arm had also been present in the pivotal clinical trial that supported the Soliris approval. This

consistent finding across two different trials using therapies with different mechanisms of action suggests that one possible explanation for this finding is that effective therapies for NMOSD do not suppress all subjective symptoms of a potential relapse event. In other words, patients may still experience symptoms consistent with relapses but lack the disabling examination findings and radiologically apparent inflammation that are present in a true relapse.

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

Table 2: Analysis of Time to AC-Confirmed NMOSD Relapse, Applicant's ITT Population

	Anti-AQP4 Antibody Positive N=213		**Anti-AQP4 Antibody Negative N=17**		**Total N=230**	
	Placebo n=52	**Inebilizumab-cdon n=161**	**Placebo n=4**	**Inebilizumab-cdon n=13**	**Placebo n=56**	**Inebilizumab-cdon n=174**
Number of Patients with a Relapse	22 (42.3%)	18 (11.2%)	0	3 (23.1%)	22 (39.3%)	21 (12.1%)
Number of Censored Patients	30 (57.7%)	143 (88.8%)	4 (100%)	10 (76.9%)	34 (60.7%)	153 (87.9%)
Hazard Ratio*		0.227		Not Applicable		0.272
95% Confidence Interval*		(0.1214, 0.4232)		Not Applicable		(0.1496, 0.4961)
p-value*		<0.0001		0.9977		<0.0001

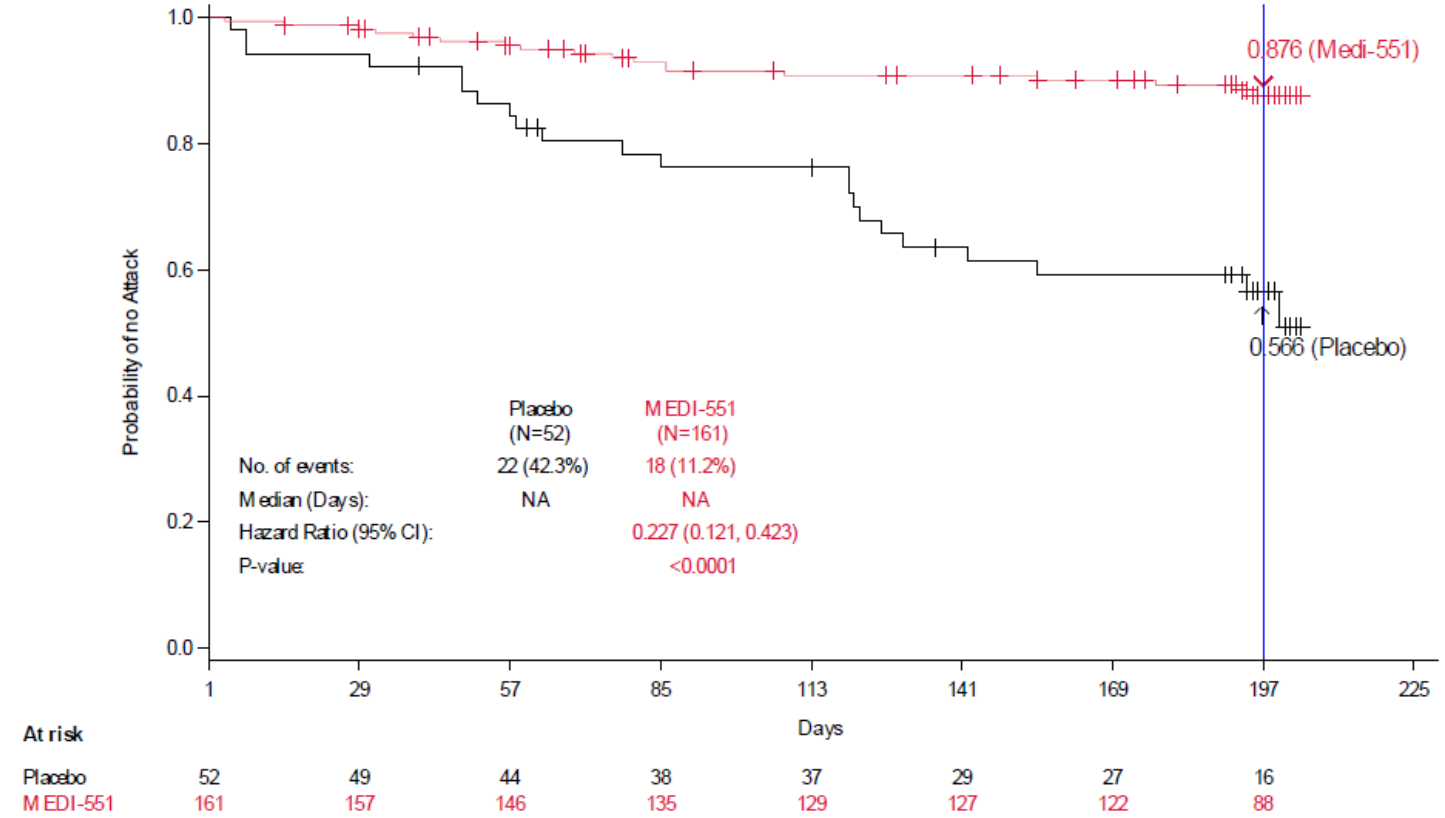
*Based on Cox regression method, with placebo as the reference group
Source: Biometrics Review

The primary efficacy analysis of Study 1155 was highly statistically significant ($p<0.0001$) in favor of inebilizumab-cdon in the anti-AQP4 antibody seropositive patients. The analysis failed to demonstrate any effect of treatment in the patients who were seronegative for anti-AQP4 antibodies ($p=0.9977$), and the overall result in all patients was clearly driven by the robust effect in the anti-AQP4 seropositive patients. Drs. Rodichok and Zhang agree that the results for the anti-AQP4 negative patients when considered separately provided no evidence of effectiveness and were not solely attributable to the relatively small number (n=17) of randomized patients. I

concur that the primary outcome analysis provides evidence of a significant treatment effect on relapses for anti-AQP4 seropositive patients but fails to provide any evidence of a treatment effect on relapses in anti-AQP4 seronegative patients.

The following figure, copied from the biometrics review, presents the Kaplan-Meier estimate to first adjudicated on-trial relapse for anti-AQP4 positive patients:

Figure 1: Kaplan-Meier Curves for Time to AC-confirmed NMOSD Relapse, Applicant's ITT Population, Anti-AQP4 Antibody Positive Patients



AQP4-IgG = autoantibodies against aquaporin-4; CI = confidence interval; MEDI-551 = inebilizumab; NA = not applicable.

Source: Biometrics Review

This figure demonstrates a statistically significant and sustained relative absence of relapses associated with inebilizumab-cdon (Medi-551 in the figure) for patients with NMOSD who are anti-AQP4 antibody seropositive. The treatment effect is evident within days of initiation of treatment with inebilizumab-cdon.

The biometrics reviewer confirmed the applicant's results from nine sensitivity analyses (including an analysis that assumed all relapses were AC-confirmed and an analysis that assumed all patients who discontinued the study had experienced an AC-confirmed relapse) demonstrating, in all outcomes, statistically significant findings (p-values ranging from <0.0001 to 0.0004) for the anti-AQP4 antibody seropositive and overall ITT populations. Subgroup analyses performed by the applicant and confirmed by the biometrics reviewer did not identify a significant treatment difference based on sex, baseline EDSS, number of prior NMOSD relapses, disease duration, or region (Japan/Non-Japan). Exploratory modelling conducted by the biometrics reviewer that assumed all censored events were AC-confirmed relapses yielded a nominal finding of significance ($p<0.03$) that further confirms the robustness of the primary analysis result for anti-AQP4 seropositive patients.

Secondary Outcome Measures

The secondary outcome measures of Study 1155 were as follows, in hierarchical order: reduction of EDSS worsening, change from baseline of low-contrast visual acuity score, reduction of the cumulative active magnetic resonance imaging (MRI) lesion count (new gadolinium-enhancing or new/enlarging T2), and reduction of NMOSD-related inpatient hospitalizations. The analysis of these secondary outcomes was conducted using a complex approach with alpha borrowing such that a failure to achieve significance on an endpoint did not preclude analysis of the next endpoint in the hierarchy (please refer to the biometrics review for details).

Change in EDSS

The following table, copied from the biometrics review, presents the results of the analysis of change from baseline in EDSS:

Table 3: Analysis of Worsening from Baseline in EDSS at the Last Recorded Visit, Applicant's ITT Population

	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
	Placebo N = 52	Inebilizumab N = 161	Placebo N = 4	Inebilizumab N = 13	Placebo N = 56	Inebilizumab N = 174
Worsening [a] from baseline in EDSS at last visit [b]	18/52 (34.6%)	25/161 (15.5%)	1/4 (25.0%)	2/13 (15.4%)	19/56 (33.9%)	27/174 (15.5%)
Odds ratio [c]		0.371		0.911		0.370
95% CI of Odds ratio [c]		(0.1807, 0.7633)		(0.0528, 15.7083)		(0.1850, 0.7389)
p-value [c]		0.0070		0.9487		0.0049

AQP4-IgG = autoantibodies against aquaporin-4; CI = confidence interval; EDSS = Expanded Disability Status Scale; ITT = intent-to-treat sero+ = seropositive; sero- = seronegative.

a A subject was considered to have a worsening in EDSS score if one of the following criteria was met: (1) Worsening of 2 or more points in EDSS score for subjects with baseline score of 0; (2) Worsening of 1 or more points in EDSS score for subjects with baseline score of 1 to 5; (3) Worsening of 0.5 points or more in EDSS score for subjects with baseline score of 5.5 or more.

b Subjects with missing data are imputed as 'worsening'. Denominator represents the total number of subjects in each group with baseline.

c Odds ratio, its 95% CI, and p-value are estimated by logistic regression model, using non-responder imputation, i.e., missing values will be considered as 'worsening'.

Source: Biometrics Review

Drs. Zhang and Rodichok note that while this analysis yields a significant finding for the applicant's ITT population and anti-AQP4 seropositive patients, there are several significant issues with the EDSS findings that make the outcome uninterpretable. These issues include the variable observation periods between patients inherent in the time-to-event trial design (which also resulted in a significant amount of missing data), a consistent lack of relapse confirmation visits at an acceptable interval, and the protocol's inadequate

approach to accounting for the impact of an acute relapse on EDSS changes from baseline. Therefore, these results do not warrant description in labeling.

Change in Low-Contrast Visual Acuity
The second item in the hierarchical analysis, the change from baseline of low-contrast visual acuity score, was not significant (p-value = 0.9736) for the applicant's ITT population and for anti-AQP4 antibody seropositive patients. The median change for both treatment arms was 0.

Cumulative Total Active MRI Lesions
The following table, copied from the biometrics review, presents the results of the analysis of cumulative number of active MRI lesions (new gadolinium-enhancing T1 or new/enlarging T2 lesions):

Table 4: Analysis of Cumulative Number of Active MRI Lesions, Applicant's ITT Population

	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
	Placebo N = 52	Inebilizumab N = 161	Placebo N = 4	Inebilizumab N = 13	Placebo N = 56	Inebilizumab N = 174
Cumulative number of active MRI lesions						
n	31	74	1	5	32	79
Mean	2.3	1.7	4.0	1.4	2.3	1.6
SD	1.3	1.0	NA	0.9	1.3	1.0
Median	2.0	1.0	4.0	1.0	2.0	1.0
(Min, Max)	(1, 5)	(1, 6)	(4, 4)	(1, 3)	(1, 5)	(1, 6)
Rate ratio[a]		0.568		0.538		0.566
95% CI		(0.3851, 0.8363)		(0.0818, 3.5462)		(0.3866, 0.8279)
p-value		0.0042		0.5198		0.0034

AQP4-IgG = autoantibodies against aquaporin-4; CI = confidence interval; ITT = intent-to-treat; max = maximum; min = minimum; MRI = magnetic resonance imaging; SD = standard deviation; sero- = seronegative; sero+ = seropositive.

a Rate ratio reduction in cumulative number of active MRI lesions. Rate ratio analysis is based on the entire population, not just those who had an event. Treatment effect and its 95% CI , and p-value are estimated from the negative binomial regression.

Source: Biometrics Review

The MRI data analysis combines gadolinium-enhancing lesions with new/enlarging T2 lesions. Typically, when reporting MRI outcomes for central nervous system lesions in clinical trials, gadolinium-enhancing lesions and new/enlarging T2 lesions are described separately because they are believed to represent two independent outcomes, with gadolinium-enhancing T1 findings being

acute inflammatory lesions and T2 lesions representing non-inflammatory later/end stage evidence of prior injury. In Study 1155, most of the lesions that were observed were gadolinium-enhancing lesions. The majority of lesions being gadolinium-enhancing is not surprising because new acute inflammatory lesions would be present in most patients with AC-confirmed relapses, and the controlled phase was relatively short, and therefore not likely to result in T2 lesions which require many months or years to evolve.

The larger issue with these MRI findings is one of clinical relevance. The confirmation of the existence of new MRI lesions in patients experiencing acute relapses in NMOSD is redundant information. If patients are not experiencing relapses, then they likely do not have new, significant MRI lesions. Although consistent with the clinical efficacy findings, the MRI data are not informative to prescribers or patients regarding outcomes expected with inebilizumab-cdon that are not already captured in a 77% relative reduction in risk of suffering a relapse. Additionally, the primary locations of lesions in NMOSD (i.e., the optic nerves, spinal cord, and brainstem) mean that new lesions are rarely “silent” or without overt impact on patients’ examinations or functional statuses. Therefore, these MRI findings should not be described in labeling.

NMOSD-related Inpatient Hospitalizations

The following table, copied from the biometrics review, presents the results of the analysis of NMOSD-related inpatient hospitalizations:

Table 5: Analysis of Number of NMOSD-related Inpatient Hospitalizations, Applicant's ITT Population

	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
	Placebo N = 52	Inebilizumab N = 161	Placebo N = 4	Inebilizumab N = 13	Placebo N = 56	Inebilizumab N = 174
Cumulative number of NMOSD-related in-patient hospitalizations						
n	7	8	1	2	8	10
Mean	1.4	1.0	1.0	1.0	1.4	1.0
SD	0.8	0	NA	0	0.7	0
Median	1.0	1.0	1.0	1.0	1.0	1.0
(Min, Max)	(1, 3)	(1, 1)	(1, 1)	(1, 1)	(1, 3)	(1, 1)
Rate ratio [a]		0.258		0.615		0.286
95% CI		(0.0904, 0.7384)		(0.0558, 6.7866)		(0.1105, 0.7411)
p-value		0.0115		0.6918		0.0100

AQP4-IgG = autoantibodies against aquaporin-4; CI = confidence interval; ITT = intent-to-treat; max = maximum; min = minimum; NMOSD = neuromyelitis optica spectrum disorders; SD = standard deviation; sero- = seronegative; sero+ = seropositive.

a Rate ratio reduction in number of NMOSD-related in-patient hospitalizations. Rate ratio analysis is based on the entire population, not just those who had an event. Treatment effect and its 95% CI , and p-value are estimated from the negative binomial regression.

Source: Biometrics Review

These data support the finding that inebilizumab-cdon significantly reduces the number of inpatient hospitalizations for patients with NMOSD who are anti-AQP4 seropositive.

Conclusions on Substantial Evidence of Effectiveness

The 2019 FDA Guidance for Industry: *Demonstrating Substantial Evidence of Effectiveness for Human Drugs and Biological Products* describes scenarios where evidence from a single clinical study can fulfill the criteria for providing substantial evidence for effectiveness under 21 CFR 314.126. Consistent with those regulations, the persuasiveness of the efficacy results from Study 1155 supports the approval of inebilizumab-cdon for the treatment of NMOSD in adult patients who are anti-AQP4 positive. Inebilizumab-cdon significantly ($p<0.0001$) reduced the relative relapse risk by approximately 77% relative to placebo in these patients, a result observed in the absence of any background therapy. This finding was supported by a number of conservative sensitivity analyses.

The findings from Study 1155 do not provide any evidence of effectiveness in patients who are anti-AQP4 antibody seronegative. Though the number of patients enrolled in the trial who were anti-AQP4 antibody negative was small, the small sample size does not appear to be the sole reason for the lack of any positive efficacy findings in this subgroup. There were no differences in the demographics or baseline disease characteristics (other than anti-AQP4 antibody status) for seronegative patients that distinguished them from the anti-AQP4 seropositive patients and could explain the lack of efficacy. Given that inebilizumab-cdon targets B-cells which secrete antibodies, it is possible this discrepancy in outcome resides in a fundamental pathophysiologic difference between the seronegative and seropositive patients in NMOSD that is evidenced by their antibody status.

The interpretable secondary outcome measures in Study 1155 further support the strength of the primary efficacy analysis in the anti-AQP4 antibody positive patients. The significant reduction in new gadolinium-enhancing lesions on MRI is consistent with a reduction in relapses which are related to new lesions in nervous tissue. The significant reduction in inpatient hospitalizations is a relevant and expected outcome for a therapy that effectively reduces the likelihood of relapses occurring. Although favoring active therapy, the applicant's analysis of the EDSS outcome is fundamentally flawed and not interpretable. There was no significant change in low visual acuity findings; however, this is not an entirely unexpected finding. Unfortunately, optic neuritis in NMOSD is devastating and yields permanent irreversible blindness so patients who experience any relapses that involve optic neuritis will have permanently diminished visual acuity that would not improve even with effective future relapse suppression.

8. Safety

Dr. Rodichok conducted the clinical safety review of Study 1155, and the open-label extension phase of Study 1155. His review noted that there were 225 patients with NMOSD who were exposed to at least one dose of inebilizumab-cdon in the applicant's NMOSD development program. Of these 225 patients, there were 174 patients who initially were randomized to receive inebilizumab-cdon in the controlled portion of Study 1155, with the remainder of the patients being those patients who were initially randomized to placebo but subsequently received inebilizumab-cdon during the open-label extension. Dr. Rodichok also reviewed safety data obtained in small controlled trials of inebilizumab-cdon in patients diagnosed with multiple sclerosis and systemic sclerosis; he found no additional safety signals to inform the NMOSD safety experience.

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

Table 6: Duration of Treatment in NMOSD Patients for Inebilizumab-cdon

Exposure Duration, years	**Safety Population**		**Anti-AQP4 IgG seropositive**	
	At submission	**At safety update**	**At submission**	**At safety update**
≤ 0.5	41	8	39	6
≥ 0.5	184	217	169	202
≥ 1	146	182	134	167
≥ 1.5	114	146	104	133
≥ 2.0	91	118	82	107
≥ 2.5	52	94	44	85
≥ 3.0	18	57	14	49
≥ 3.5	3	23	2	18
≥ 4.0	0	7	0	5

Source: Clinical Review

As indicated in the previous table, at the time of the safety update to the application, there were 182 patients with at least a year of exposure, and 167 of these patients with at least a year of exposure were anti-AQP4 positive. In the overall trial population, most of the patients (greater than 90%) were women and over 70% were White or Asian, which conforms to the expected demographics for a

NMOSD population. Dr. Rodichok concluded that the safety database for NMOSD, and for NMOSD patients with anti-AQP4 antibodies, was adequate to support meaningful conclusions. I concur with his conclusion that the safety database for inebilizumab-cdon is adequate.

Deaths

There were two deaths that occurred in the clinical development program for NMOSD. These deaths occurred in the open-label extension phase of Study 1155; there were no deaths during the controlled study phase of the trial.

The first death in the program was a 31-year-old man with NMOSD who had been randomized to placebo and experienced a protocol-defined relapse on Study Day 29. As a result of the relapse, manifesting as worsening leg weakness and a loss of bladder control, his EDSS increased to 8.0. After a course of IV high-dose steroids, the patient entered the open-label extension phase and received his first dose of inebilizumab-cdon on Study Day 52. Routine laboratory studies obtained on that date revealed no abnormalities. Seven days later (Study Day 59), he was reportedly weak and had a poor appetite. On Study Day 61, his caregiver found him unresponsive and apneic in bed. He was pronounced dead shortly thereafter. There was no autopsy. Dr. Rodichok reviewed the case and concluded that despite the patient's demise occurring within ten days of his first dose of inebilizumab-cdon, there were no findings to suggest a relationship between inebilizumab-cdon and the sudden death. He postulated that the patient's advanced disability coupled with another relapse, perhaps in the brainstem, signaled by the reported low appetite and increased weakness, were more likely causes of death.

The second death in the program was a 68-year-old woman with NMOSD who was randomized to inebilizumab-cdon and was treated for seven months until entering the open-label phase after a confirmed episode of optic neuritis. Following treatment with high-dose IV methylprednisolone, she was evaluated to follow-up her relapse status and found to be at her trial baseline neurological function. She received her next dose of inebilizumab-cdon five days after the follow-up visit for optic neuritis. Three days after receiving treatment, she was hospitalized with altered mental status and increased weakness. She became progressively less interactive during the hospitalization, was no longer speaking, and had new diffuse right-sided weakness. Seizures and decorticate posturing followed. Neuroimaging at admission revealed a new lesion in the left fronto-parietal region with follow-up higher resolution imaging describing a large gadolinium-enhancing hyperintense lesion in the inferior frontal region. These lesions had not been present in her optic neuritis follow-up imaging obtained just eight days prior to this hospital admission. Progressive multifocal leukoencephalopathy (PML) was suspected as a diagnosis. An initial JC virus assay was positive, but subsequent follow-up testing, using two more sensitive assays, was negative. The patient died from respiratory arrest approximately one month after admission. Dr. Rodichok reviewed all records available for this case and concluded there were many features consistent with probable PML with only the discrepancy in JC virus testing results being an argument against definite PML. He concluded that the death was not clearly related to

inebilizumab-cdon but could be secondary due to an opportunistic infection, probable PML, in the setting of immune suppression. He recommended a labeling warning for PML.

I concur with Dr. Rodichok's conclusions regarding both deaths. Despite the relative proximity of inebilizumab-cdon infusion to death in both cases, there are no findings to suggest a post-infusion reaction or direct consequences of these infusions were causes of these deaths. In the first death, the patient had symptoms suggestive of a significantly debilitated bedridden patient that may have had a brainstem lesion in evolution that compromised his respiratory drive, an uncommon but known cause of death in patients with NMOSD. In the second death, there is a high degree of suspicion that the patient had PML, or a new rapidly evolving brain lesion due to another opportunistic infection or, much less likely, an atypical NMOSD brain lesion. The PD effect of inebilizumab-cdon reduces B-lymphocyte levels and is similar to other therapies associated with a risk of PML. Based on this case, I agree with the need for a labeling warning for PML and other opportunistic infections. A risk of a serious opportunistic infection such as PML in a therapy for NMOSD would not preclude approval given that NMOSD is a serious, potentially fatal disease with only one established effective therapy.

Serious Adverse Events

Eight patients (4.6%) treated with inebilizumab-cdon experienced a total of ten serious adverse events during the controlled phase of Study 1155. Dr. Rodichok noted this is a seemingly low number of serious adverse events and suggested that the relatively short average exposure duration (approximately six months) of patients in the controlled phase of the trial, and the small patient pool, as possible explanations. The serious adverse events were isolated cases of blurry vision, diarrhea, acute cholangitis, acute cholecystitis, abnormal hepatic function, atypical pneumonia, myelitis, urinary tract infection, third degree burn, and arthralgia. Dr. Rodichok noted that these serious events included a cluster of serious infectious events (atypical pneumonia, urinary tract infection, acute cholangitis with cholecystitis and abnormal hepatic function), but a risk of serious infections is expected with a therapy that reduces B-cells based on prior experience with similar therapies. He recommended that 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. He noted several serious adverse events were consistent with NMOSD-related sequelae (blurry vision, myelitis, arthralgia) and therefore likely unrelated to treatment. An analysis limited to just anti-AQP4 antibody positive patients did not change the overall safety conclusions for the indicated population.

Interruptions and Discontinuations

Two patients (0.9%) discontinued/interrupted study treatment in the controlled trial due to adverse events; both patients were being treated with inebilizumab-cdon. One patient discontinued due to atypical pneumonia and another due to myasthenia gravis.

As with the serious adverse event number, a discontinuation rate of less than 1% is low but likely so because of the small study population combined with a time-to-event trial design resulting in a short duration of blinded trial treatment.

Treatment-Emergent Adverse Events
The following table summarizes the most common adverse events that occurred in the controlled phase of Study 1155:

Table 7: Treatment Emergent Adverse Events During Controlled Phase of Study 1155 Occurring in Greater Than 2% of Patients Treated with Inebilizumab-cdon and Greater Than Placebo

Dictionary Derived Term	**Inebilizumab-cdon (n=125)**	**Placebo (n=56)**
Urinary tract infection	20 (12%)	5 (9%)
Arthralgia	17 (10%)	2 (4%)
Headache	13 (8%)	4 (7%)
Back pain	13 (8%)	2 (4%)
Fall	8 (5%)	1 (2%)
Hypoesthesia	6 (3%)	1 (2%)
Cystitis	5 (3%)	0 (0%)
Eye pain	5 (3%)	1 (2%)
Oropharyngeal pain	4 (2%)	1 (2%)
Paresthesia	4 (2%)	0 (0%)
Rash	4 (2%)	0 (0%)
Neutropenia	4 (2%)	0 (0%)

Source: Clinical Review

As the table demonstrates, overall, inebilizumab-cdon was well-tolerated. Most of the adverse events occurring relatively more often in association with inebilizumab-cdon (e.g., urinary tract infection, pain phenomena) are treatable and are not usually life-threatening. Falls and neutropenia are potentially serious adverse events that are amenable to awareness and monitoring.

Infusion-related reactions were slightly more common in placebo-infused patients (11% versus 9%). There were no serious or fatal infusion-related reactions in Study 1155 suggesting that infusions of inebilizumab-cdon, with appropriate premedication and observation, are relatively well-tolerated.

Several pain-related terms (arthralgia, eye pain) were also reported at higher rates in eculizumab-treated patients in the Soliris development program for NMOSD. The explanation for an apparent higher reported rate of painful phenomena in the active treatment arms from two different therapies' placebo-controlled trials is unclear. Pain is a manageable symptom and was not ever cited as a reason for discontinuation of therapy in either the inebilizumab-cdon or eculizumab trials.

Dr. Rodichok reviewed treatment-emergent adverse events in just anti-AQP4 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 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 PML, infections, infusion-related reactions, and immunosuppression. The risks of infections, PML, and infusion-related reactions are largely discussed above.

Infection Risk
In addition to the risk of infections discussed above, including the potential for serious infections, hepatitis B infection can reactivate in patients treated with therapies with mechanisms of action similar to inebilizumab-cdon, and so a warning regarding adequate assessment of hepatitis B history will be included in labeling. The clinical trial specifically excluded patients with a history of tuberculosis (TB), and so a warning for adequate treatment of patients with a prior history of TB will be included, as well.

Immunosuppression
Patients treated with inebilizumab-cdon have significantly reduced levels of CD19+ B-lymphocytes. Since CD19 expression occurs early in B-cell maturation, over time, inebilizumab-cdon causes a decrease in all B-cell subtypes, including B-cells that secrete antibodies. Not surprisingly, the quantity of antibodies, measured as serum immunoglobulins, in patients treated with inebilizumab-cdon in Study 1155 steadily decreased with chronic use such that in two patients observed for 208 weeks there was a median decrease of over 50% in total serum immunoglobulin from their baseline. The combination of diminished B-cells and immunoglobulins could lead to clinically significant immunosuppression. There was a patient in the NMOSD development program who was identified as having recurrent pneumonia with fungal opportunistic organisms who required immunoglobulin infusions to treat hypogammaglobulinemia. Dr. Rodichok concluded that the downward trend observed in immunoglobulins had not reached a clear plateau and was concerned that more observation time was needed to identify if there was a nadir or whether most patients, given sufficient exposure duration, would become hypergammaglobulinemic. I concur with his recommendation that a postmarketing study is needed to identify the long-term consequences of B-cell depletion associated with inebilizumab-cdon. The goal of this

postmarketing requirement would be to identify whether the immunoglobulin levels in patients reach a consistent nadir, to identify whether there are more patients who may require exogenous immunoglobulins to treat hypogammaglobulinemia and recurrent opportunistic infections, and to identify the timetable for recovery of immunoglobulins in patients who discontinue therapy.

The postmarketing requirement for a pregnancy registry will also evaluate immunosuppression because of an observation in animal models that offspring of animals exposed to inebilizumab-cdon in utero had reduced antigenic responsiveness as adults. There is one known inebilizumab-cdon human pregnancy exposure with a reportedly healthy birth, but other B-cell depleting therapies have been reported to cause transient depletion of B-cells in newborns. Further study is therefore needed to establish if inebilizumab-cdon exposure may permanently alter the immune response in children born to mothers receiving inebilizumab-cdon because many of the patients worldwide with NMOSD will be women of childbearing potential.

Safety Conclusions

Inebilizumab-cdon is associated with adverse reactions, some of which are serious. 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 effect of effective therapies of unclear significance and etiology. Otherwise, the identified risks are consistent in frequency and type with other approved therapies that deplete B-cells used in other serious indications such as multiple sclerosis and hematologic malignancies. The safety profile of inebilizumab-cdon is acceptable for the treatment of NMOSD, a serious, potentially fatal, disease. Postmarketing requirements to evaluate the extent of immunosuppression and potential immune effects on offspring exposed in utero are needed to provide additional data to inform the safety of inebilizumab-cdon longitudinally and in women of childbearing potential who comprise a majority of the expected indicated 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 the other drugs with similar mechanisms approved for other indications, the clinical trial design was 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 fully aware of the risks associated with inebilizumab-cdon treatment, allowing them to inform patients and decide whether to use the drug.

10. Pediatrics

NMOSD is rare in children and adolescents. In addition, this development program has orphan drug designation, and is exempt from PREA requirements.

11. Other Relevant Regulatory Issues

- The review of this application did not identify any Good Clinical Practice (GCP) issues.
- Dr. Rodichok concludes that the applicant has adequately disclosed financial interests and arrangements with the clinical investigators.
- The Office of Scientific Investigations (OSI) completed inspections of three investigators' sites (Drs. Cree, Pardo-Villamizar, and Villegas) and did not identify any significant issues.
- The Division of Risk Management (DRM) did not recommend a REMS for inebilizumab-cdon.

12. Labeling

Please refer to the final negotiated product label.

13. Postmarketing Recommendations

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The following are postmarketing requirements:

- 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 Uplizna (inebilizumab-cdon) during pregnancy in patients with neuromyelitis optica spectrum disorder (NMOSD). Provide a complete protocol which includes details regarding how you plan to encourage patients and providers to report pregnancy exposures (e.g., telephone contact number and/or website in

prescribing information), measures to ensure complete data capture regarding pregnancy outcomes, and any adverse effects in offspring and plans for comprehensive data analysis and yearly reporting.

Draft Protocol Submission:	12/2020
Final Protocol Submission:	08/2021
Annual Interim Report Submissions:	08/2022
	08/2023
	08/2024
	08/2025
	08/2026
	08/2027
	08/2028
	08/2029
	08/2030
	08/2031
Study Completion:	08/2032
Final Report Submission:	08/2033

- A safety trial to monitor serum immunoglobulin G and M levels in patients with neuromyelitis optica spectrum disorder (NMOSD) during treatment with Uplizna (inebilizumab-cdon) to establish the nadir in circulating immunoglobulins during chronic treatment, and to monitor patients after discontinuation of treatment with Uplizna (inebilizumab-cdon) in order to ascertain the time needed to ensure restoration of pre-treatment baseline circulating serum levels of immunoglobulins G and M. This trial also should be designed to capture rates of infections, especially opportunistic and recurrent infections associated with immune suppression, and there should be monitoring B-cell counts throughout treatment and after discontinuation until repletion of immunoglobulin levels.

Draft Protocol Submission:	12/2020
Final Protocol Submission:	08/2021
Study/Trial Completion:	08/2027
Final Report Submission:	08/2028

The following is a postmarketing commitment:

- A shipping study to confirm stability of Uplizna (inebilizumab-cdon) drug substance during shipping under conditions and through a route (b) (4). The study will include monitoring of temperature during three shipments covering the drug substance bag fill range and testing of post-shipping materials for product quality against applicable approved drug substance release acceptance criteria.

Draft Protocol Submission:	12/2020
Final Protocol Submission:	06/2021
Study/Trial Completion:	06/2022
Final Report Submission:	12/2022

14. Recommended Comments to the Applicant

There are no additional recommended comments to the applicant.

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/

PAUL R LEE
06/11/2020 01:40:37 AM

NICHOLAS A KOZAUER
06/11/2020 07:48:23 AM

WILLIAM H Dunn
06/11/2020 01:03:11 PM