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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review
Lawrence Rodichok MD
BLA 761149
Enspryng/satralizumab-mwge

CLINICAL REVIEW

Application Type	BLA
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Division/Office	DN2/Office of Neuroscience
Reviewer Name(s)	Lawrence Rodichok MD
Review Completion Date	5/28/20
Established/Proper Name	Satralizumab-mwge (b) (4)
(Proposed) Trade Name	Enspryng
Applicant	Roche/Genentech
Dosage Form(s)	Injection:120mg/mL in a single-dose prefilled syringe
Applicant Proposed Dosing Regimen(s)	120 mg subcutaneous at Weeks 0, 2 and 4, and every 4 weeks (Q4W) thereafter
Applicant Proposed Indication(s)/Population(s)	Adult (b) (4) with NMOSD.
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

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Glossary

AC	advisory committee
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	Analysis of Covariance
AQP4	aquaporin-4
AST	aspartate aminotransferase
AR	adverse reaction
ARR	annualized relapse rate
AUC	Area under the curve
BAFF	B-cell activating factor
BLA	biologics license application
BLyS	B-lymphocyte stimulating factor
BOCF	baseline observation carried forward
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BUN	blood urea nitrogen
Ca	calcium
CBER	Center for Biologics Evaluation and Research
CD	Cluster of Differentiation
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CEC	clinical events committee
CFR	Code of Federal Regulations
CK	Creatine Kinase
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CRT	clinical review template

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CSR	clinical study report
CSS	Controlled Substance Staff
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	diastolic blood pressure
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EDSS	Expanded Disability Status Scale
eCTD	electronic common technical document
ELISA	enzyme-linked immunosorbent assay
EQ-5D	European Quality of Life – 5 Dimensions
ETASU	elements to assure safe use
EU	European Union
FACIT	Functional Assessment of Chronic Illness
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FSS	Functional System Score
GCP	good clinical practice
GRMP	good review management practice
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDMC	independent data monitoring committee
IEC	Independent ethics committee
IgG	immunoglobulin
IL-6	interleukin-6
IL-6R	interleukin-6 receptor
IMP	investigational medical product
IND	Investigational New Drug Application
IRB	institutional review board
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
IVIG	intravenous immune globulin
LCSLC	low contrast Sloan letter chart
LDH	lactate dehydrogenase

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LDL	low density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MRI	magnetic resonance imaging
mRS	modified Rankin scale
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NMO	Neuromyelitis Optica
NMOSD	Neuromyelitis Optica Spectrum Disorder
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PML	progressive multifocal leukoencephalopathy
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
Q4W	every 4 weeks
QTcF	QT interval corrected for heart rate by Fridericia's formula
RA	Rheumatoid Arthritis
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SGE	special government employee
SOC	System Organ Class
TEAE	treatment emergent adverse event
T25FW	Timed 25-foot walk test
TFR	Time to first relapse

1. Executive Summary

1.1. Product Introduction

Satralizumab-mwge, also known as SA237, is a humanized anti-interleukin- 6 receptor (IL-6R) monoclonal antibody. It is a recombinant humanized monoclonal antibody based on a human immunoglobulin G2 (IgG2) framework containing heavy chain V_H and light chain V_k subgroup sequences. (b) (4)

The recombinant humanized monoclonal antibody is produced in Chinese hamster ovary (CHO) cells and consists of two heavy chains (443 amino acid residues each), and two light chains (214 amino acid residues each). The calculated molecular mass of intact satralizumab-mwge is 143, (b) (4) Daltons (peptide chains only).

1.2. Conclusions on the Substantial Evidence of Effectiveness

There is substantial evidence from two independent, adequate and well-controlled trials that treatment with satralizumab-mwge prolongs the time to relapses in adult patients with Neuromyelitis Spectrum Disorders (NMOSD) who are seropositive for anti-aquaporin-4 (AQP4) antibodies. The two trials were similar in design with the exception that one allowed concurrent treatment with one immunosuppressant drug and the other study allowed treatment with either satralizumab-mwge or placebo only. For the primary endpoint of the time to first adjudicated relapse, the two studies showed a similar benefit. The result is supported by the proportion of subjects who were free of relapses at the end of the controlled treatment phase of the study. There was no benefit in either study on measures of fatigue or pain. Nevertheless, the delay and overall reduction in relapses are clinically important benefits.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The substantial evidence of safety and efficacy is based on the results of two adequate and well-controlled clinical trials of treatment with satralizumab-mwge compared to placebo in patients with NMOSD. Benefit is limited to NMOSD patients who are anti-AQP4 IgG seropositive. Approximately 30% of the subjects were anti-AQP4 IgG seronegative; there is no indication of a benefit in that subgroup in either study. The evidence of benefit on reduction of relapses in patients who are anti-AQP4-IgG seropositive is demonstrated in both clinical trials. Although analysis of some secondary endpoints is limited by the time-to-event design, these results are generally supportive of the primary analysis. The characteristics of the subjects from outside the US and the results in those populations support translation of the overall results to the US population of NMOSD patients. The data on the safety of satralizumab-mwge are adequate to support a positive benefit to risk comparison. However, there are very limited previous safety data on the use of satralizumab-mwge. Therefore, continued safety surveillance, including surveillance of infections and of complement levels, following approval will be important to an ongoing assessment of the benefit to risk comparison. Overall, the benefit to risk comparison justifies approval of the application.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	- NMOSD is associated with recurrent attacks that predominantly involve the spinal cord and optic nerves - NMOSD attacks can result in severe and largely irreversible neurologic disability, including loss of independent ambulation, loss of vision, and death from respiratory failure - The spectrum of the severity of attacks in patients with NMOSD is uncertain. Although some attacks may be very severe, others may result in mild or moderate and reversible disability.	Given the severity of many NMOSD attacks, a reduction in the occurrence of relapses is clinically relevant.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	Soliris was been approved in 2019 for the treatment of anti-AQP4-IgG seropositive NMOSD patients. Uplizna has subsequently been approved for the treatment of anti-AQP4-IgG seropositive NMOSD patients. These are the only two drugs approved in the US for the treatment of NMOSD	The mechanism of action of Enspryng is distinct from that of Soliris and Uplizna and may, therefore, add an important alternative treatment for NMOSD. In addition, Enspryng would provide an alternative to patients who are allergic or unable to tolerate Soliris or Uplizna
Benefit	The time to the Clinical Events Committee (CEC)-confirmed NMOSD relapse was significantly prolonged in both trials. This evidence of benefit is limited to adult patients who are anti-AQP4 IgG seropositive. There is relatively little uncertainty regarding this benefit. There is no indication of a benefit on short term disability. It is uncertain whether the reduction in relapses will translate to a benefit on longer-term irreversible disability.	The demonstrated reduction in relapses is clinically relevant and offers a meaningful benefit to NMOSD patients.
Risk and Risk Management	The most important risk is that of infections. No specific type of infection appeared to be prominent in the clinical trials. Tocilizumab and sarilumab are very similar biologics and both have a black box warning for serious infections although this may in part reflect the population for which they are indicated. The size of the population treated with satralizumab-mwge is relatively limited. The risks could increase with longer term use in a larger and more diverse population after approval.	Continued safety surveillance, especially for serious infections, is feasible and should mitigate the risks of satralizumab-mwge treatment in NMOSD patients.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

☐	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
☐	Clinical outcome assessment (COA) data	6.1.2, 6.2.2
☒	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	

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☐	Other:	
☐	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Neuromyelitis Optica (NMO) is an inflammatory disorder of the central nervous system characterized clinically by recurrent attacks that most commonly affect the optic nerves and spinal cord. Many clinicians originally considered NMO to be an unusually severe and limited form of Multiple Sclerosis (MS). When first recognized as a distinct clinical syndrome, a diagnosis of NMO, also known as “Devic’s syndrome”, was considered if acute bilateral optic neuritis and acute transverse myelitis occurred concurrently or within a short period of time of each other, typically resulting in near total loss of vision and/or paraplegia. Although NMO was originally considered a monophasic illness, it was recognized that relapses were seen in up to 90% of patients. In an early review of cases of NMO from the Multiple Sclerosis program at Mayo Clinic, Wingerchuk et al.¹ expanded the “strict” definition to include cases of bilateral optic neuritis and myelitis that had occurred within 2 years of each other, and in which there was no indication of disease elsewhere in the nervous system. The group meeting the strict criteria was compared to patients who did not meet these strict criteria but whose optic neuritis attack was unilateral and/or whose attacks occurred over a period of greater than 2 years. Of the 71 patients reviewed, 23 had had a “monophasic” course, i.e. qualifying attacks occurred over a median period of 5 days with no further attacks after a minimum period of 3 years follow-up, and 48 had a “relapsing” course, i.e. there were additional attacks. The clinical characteristics of these two groups did not differ. For the relapsing group, the next attack occurred within 1 year in 55%, within 3 years in 78% and within 5 years in 90%. The severity of the attacks appeared to be much worse in comparison to MS relapses. Functional blindness and permanent monoplegia or paraplegia were not uncommon on long-term follow-up. Respiratory failure due to cervical myelitis occurred in about one-third of relapsing patients resulting in death in 15/16 patients. NMO was also distinguished from MS by the relative absence of MRI changes in the brain. A cerebrospinal fluid (CSF) pleocytosis was more common in NMO patients and oligoclonal immunoglobulin bands in the CSF were typically absent. A phase of slowly progressive disability independent of relapses is common in MS but very uncommon in NMO where disability is largely due to incomplete recovery from the individual attacks². In Asia, an “optico-spinal” form accounted for up to 40% of MS but was similar clinically to NMO^{3,4}. Subsequent refinements in the diagnostic criteria for NMO were based on clinical and imaging features but distinction from MS was not reliable. However, an IgG antibody that was described initially by Lennon et al.⁵ appears to be specific for patients with NMO. This antibody is not found in patients with MS. “NMO IgG” binds to aquaporin 4 (AQP4), the predominant water channel protein in the central nervous system (CNS). AQP4 is expressed prominently on astrocytic endfoot processes at the blood brain barrier in brain and spinal cord. It is also

prominent in the subependymal region and in the floor of the 4th ventricle⁶. AQP4 immunoreactivity is not detectable in NMO lesions regardless of the stage of demyelination whereas this is the case only for inactive, usually chronic MS lesions. AQP4 immunoreactivity is increased at the perimeter of active areas of demyelination in MS. In NMO there may also be areas in the spinal cord and brainstem that show no evidence of demyelination but contain eosinophil and plasma cell infiltrates with perivascular deposits of IgG, IgM and complement activation products⁶. This provides a rationale for the development of products that target either B cells (e.g. rituximab) or complement (e.g. eculizumab) for the treatment of NMO. Interleukin-6 (IL-6) is a cytokine that functions in both the innate and adaptive immunity. It is produced by multiple cell types including activated mononuclear phagocytes. IL-6 stimulates the synthesis of acute phase proteins and the generation of antibody-producing B-lymphocytes. Elevated levels of IL-6 have been found in the cerebrospinal fluid of patients during an NMOSD attack but not in patients with an MS relapse⁷. The elevated levels of IL-6 have been shown to enhance the survival of anti-AQP4 antibody producing plasmablasts⁸. This provides a rationale for the study of drugs that act at the IL-6 receptor for the treatment of NMOSD.

It is important to accurately distinguish NMO from MS because there are significant differences between NMO and MS in the approach to the treatment of acute attacks and the prevention of attacks. Furthermore, early intervention may be more critical for NMO because the prognosis for NMO has been considered much worse than that for MS.

A serum antibody to aquaporin-4 appears to be specific for NMO and is found in most Japanese patients with opticospinal MS who meet the clinical criteria for NMO⁵. The sensitivity of the original indirect immunofluorescence assay in clinical NMO patients was 73% (95%CI: 60-86) and specificity was 91% (79-100%)⁵. For the Asian opticospinal MS, the sensitivity was 58% (30-86) and the specificity was 100% (66-100). There is wide variability in the sensitivity and specificity of the assays for anti-AQP4 antibody⁹. Some patients in whom the anti-AQP4 antibody is not found may test positive for an anti-myelin oligodendrocyte glycoprotein antibody (MOG). The clinical manifestations of CNS disease related to anti-MOG antibodies may be similar to that of NMOSD¹⁰. The presence of the anti-AQP4 antibody is now a key criterion in the most recent criteria for the diagnosis of NMOSD¹¹.

Reviewer Comment: See the review comment prior to [Table 12](#) regarding the method of detection of anti-AQP4 antibody in the trials submitted in this application.

2.2. Analysis of Current Treatment Options

Prior to the approval of Soliris® on 6/27/19, there had been no approved treatments for NMOSD. Uplizna was approved on 6/11/20. Prior to those approvals, drugs that had been approved for other indications and that targeted some aspect of the immune system that was perceived to be appropriate for the treatment of NMOSD were most commonly used for the treatment of NMOSD. Rituximab is a chimeric murine/human monoclonal antibody directed against the CD20 antigen. It is approved for the treatment of several autoimmune inflammatory disorders such as Rheumatoid Arthritis. Rituximab has been reported in uncontrolled studies to reduce the attack rate in NMOSD¹²⁻¹⁷. Following the initial treatment course, patients may be retreated when CD19+ cells reach a certain threshold or for recurrent attacks. Safety concerns include those typical of most drugs that suppress the immune system along with serious infusion reactions, reactivation of hepatitis B virus and the possibility of progressive multifocal leukoencephalopathy (PML). Azathioprine (AZA) is a purine anti-metabolite approved for the treatment of RA. It has also been reported in uncontrolled studies to reduce the attack rate to nearly zero per year^{18,19}. In addition to the risks due to immune suppression, AZA carries a black box warning for an increased risk of malignancies. Mycophenolate, an antimetabolite immunosuppressant generally used for suppression of rejection in transplant recipients, has also been used to prevent NMOSD relapses^{20,21} with a relapse rate reduction comparable to that with AZA and rituximab.

Table 1: Approved and commonly used unapproved treatments for NMOSD

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed)
FDA approved treatments						
Soliris	Treatment AQP4 positive (NMOSD) in adults	2019	900 mg IV weekly X 4, followed by 1200 mg for the 5 th dose one week later, then 1200 mg every 2 weeks thereafter	Reduction by 96% in Annualized Relapse Rate	Black box warning for meningococcal infections	
Uplizna	Treatment AQP4 positive (NMOSD) in adults	2020	300 mg IV, initial dose and 2 weeks later, then 300 mg IV q6months	Reduction by 77% in Annualized Relapse Rate	Increased risk of serious infections; reduction in immunoglobulin levels	
Other Treatments						
Rituximab	RA, GPA, MPA, PV*	1997	375 mg/m ² IV qweek X4	No controlled trials	Infection, infusion reactions	
Azathioprine	RA	1968	100 mg po qd	No controlled trials	Infection, malignancy	
Mycophenolate	Transplant rejection	1995	1000 mg/day	No controlled trials	Infection, malignancy	

*: RA: Rheumatoid arthritis, GPA: Granulomatosis with polyangiitis; MPA: microscopic polyangiitis; PV: pemphigus vulgaris

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

There has been no previous regulatory action on satralizumab-mwge. Satralizumab-mwge is not marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

Original IND: 9/19/13

CDER Clinical Review Template

Version date: September 6, 2017 for all NDAs and BLAs

Clinical Review
Lawrence Rodichok MD
BLA 761149
Enspryng/satralizumab-mwge

Grant Fast Track: 10/31/13
Orphan Drug Designation: 6/30/14
SPA Agreement (Study 309): 10/17/14
Breakthrough therapy designation: 12/18/18
Pre-BLA meeting: 7/1/19

3.3. Foreign Regulatory Actions and Marketing History

The sponsor reports no regulatory action for satralizumab-mwge. Satralizumab-mwge is not currently marketed in any country. The EMA did receive a marketing application for satralizumab-mwge in September 2019.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Two sites were inspected by the FDA (b) (4). The sites inspected by the FDA both participated in study 309. Site 2451 randomized and treated 3 subjects, and site 2515 randomized and treated 5 subjects. "The study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication."

(b) (4)

4.2. Product Quality

See the CMC reviews

4.3. Clinical Microbiology

See the CMC reviews

4.4. Nonclinical Pharmacology/Toxicology

See the review by Dr. David Hawver. Of note is a finding of reduced levels of IgG and IgM in

CDER Clinical Review Template

Version date: September 6, 2017 for all NDAs and BLAs

infants of cynomolgus monkeys treated with satralizumab-mwge.

“In the ePPND study, administration of satralizumab-mwge (0, 2, and 50 mg/kg/week SC) to pregnant females resulted in a dose-dependent reduction in the antibody responses to antigenic challenge in infants. Median maximum titers of IgM and IgG were reduced 15% and 16%, respectively, in low-dose infants, and 30% and 50%, respectively, in high-dose infants. A no-effect level was not established. This immunosuppressive effect was not unexpected in view of the intended pharmacological effects of satralizumab-mwge to inhibit the survival and function of plasmablasts. However, infants of women treated with satralizumab-mwge during pregnancy may be at increased risk of adverse effects such as infection or impaired response to vaccinations.”

4.5. Clinical Pharmacology

See the Office of Clinical Pharmacology integrated review.

4.6. Devices and Companion Diagnostic Issues

There are no device issues.

See the comment above [Table 12](#) regarding the assay for the anti-AQP4 antibody.

Reviewer Comment: Because there is no indication of a benefit of satralizumab-mwge treatment in patients with NMOSD who are not seropositive for the anti-AQP4 antibody, the labelled indication will be limited to seropositive patients. The sponsor has provided a test for the antibody that has been cleared by CDRH.

4.7. Consumer Study Reviews

There were no consumer study reviews.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Trial Identifier	Design	Dose regimen	Endpoints	Treatment duration	Number treated	Population
Controlled Clinical Studies						
BN40900 (SA-309JG)	Placebo-controlled RCT	Satralizumab-mwge 120 mg / placebo at Week 0, 2 and 4 then satralizumab-mwge 120 mg / placebo SC Q4W	Primary: Time to the onset of a CEC-confirmed NMOSD attack	To first relapse or CCOD*; maximum 1.5 years	SA237: 63 PBO: 32	NMOSD, AQP4 positive and negative
BN40898 (SA-307JG)	Placebo-controlled RCT	Same as Study 309	Same as Study 309	To first relapse or end of RCP; maximum 1.5 years	SA237: 42 PBO: 41	NMOSD, AQP4 positive and negative; up to 7 who were 10 to 17 years old
Studies to Support Safety						
SA-001JP	SAD	30-240 mg SC	Safety	Single dose	PLACEBO:12 SA237: 72	Healthy Volunteers
SA-105JP	MAD	30-120 mg SC	Safety	Single dose	SA237: 33	Rheumatoid Arthritis
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
No other clinical studies						

*: CCOD: Clinical Cut-off Date

5.2. Review Strategy

A Special Protocol Assessment (SPA) agreement was granted for Study 309 and, therefore, it is the first study reviewed. Potentially confounding concurrent immunotherapy was not allowed in study 309. The use of concurrent immunotherapy in Study 307 may confound interpretation of both efficacy and safety. Therefore, the results of Study 307 may be considered supportive of the Study 309 result. Both studies use the same objective criteria for a clinically relevant worsening in neurologic deficit that define a relapse. These criteria were part of the SPA agreement and are listed in [13.6](#).

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 309JG; bn40900. A Multicenter, Randomized, Double-Blind, Placebo-controlled Study To Evaluate The Efficacy And Safety of Satralizumab-mwge (SA237) As Monotherapy In Patients With Neuromyelitis Optica (NMO) and Neuromyelitis Optic Spectrum Disorder (NMOSD)

6.1.1. Study Design

Overview and Objective

The primary objective of this study was to evaluate the efficacy and safety of satralizumab-mwge compared to placebo in patients with NMOSD who were not being treated with concurrent immunosuppressant or immunomodulating drugs.

Reviewer Comment: Following discussions with the Division of Neurology Products regarding the design of a pivotal study, this protocol was granted an SPA agreement. Unlike Study 307JG, patients were not being treated with concurrent immunotherapies that might confound interpretation of the results.

Trial Design

Study 309JG was a multicenter randomized, double-blind, placebo-controlled parallel assignment study. Approximately 90 patients were to be randomized 2:1 to treatment with either subcutaneous satralizumab-mwge or placebo at Weeks 0, 2 and 4, and Q4W thereafter. The study intended to limit the number of patients who were negative for anti-AQP4 IgG antibody at screening to 30% of total study population. Randomization was stratified by prior therapy for prevention of NMO/NMOSD attack (B-cell depleting therapy vs. other immunosuppressants or other therapies) and by the most recent attack in the last one year prior to screening (first attack or relapse). Subjects who experienced a relapse adjudicated by the Clinical Events Committee (CEC) or completed the blinded treatment phase without a relapse were eligible to be treated with satralizumab-mwge in an open-label extension period. Subjects were treated to the time of a confirmed relapse or until the end of the randomized-controlled phase (RCP) of the trial. The maximum duration of treatment was limited to 1.5 years. For and individual subject, the end of the RCP was the day before the subject received 1st dose in the Open Label Extension (OLE) or until the withdrawal visit. For the study, the RCP continued after the Clinical Cutoff Date (CCOD) until all patients had received their first dose in the OLE period or withdrew.

Eligibility

Inclusion criteria

1. Patients must be diagnosed as either:
 - a. NMO as defined by Wingerchuk 2006 criteria^{22*}, or
 - b. NMOSD as defined by either of following criteria with anti-AQP4 antibody seropositive status at screening.
 - i. Idiopathic single or recurrent events of longitudinally extensive myelitis (≥ 3 vertebral segment spinal cord MRI lesion)
 - ii. Optic neuritis, single, recurrent or simultaneous bilateral
2. Clinical evidence of at least 1 documented relapse (including first attack) in the last 12 months prior to screening.
3. EDSS score from 0 to 6.5 inclusive at screening.
4. Age 18 to 74 years, inclusive at the time of informed consent.
5. Ability and willingness to provide written informed consent and to comply with the requirements of the protocol.

*According to Wingerchuk et al. 2006, a diagnosis of NMO requires all of following criteria:

- I. Optic neuritis
- II. Acute myelitis
- III. At least two of three supportive criteria:
 - Contiguous spinal cord lesion identified on an MRI scan extending over 3 vertebral segments
 - Brain MRI not meeting diagnostic criteria for multiple sclerosis
 - NMO-IgG seropositive status

Exclusion criteria

Exclusion Criteria Related to Neuromyelitis Optica:

1. Clinical relapse onset (including first attack) within 30 days prior to baseline.

Exclusion Criteria Related to Previous or Concomitant Therapy:

2. Any previous treatment with IL-6 inhibitory therapy (e.g., tocilizumab), alemtuzumab, total body irradiation or bone marrow transplantation at any time.
3. Any previous treatment with anti-CD20, eculizumab, anti-B-Lymphocyte Stimulator (BLyS) monoclonal antibody (e.g., belimumab), any other treatment for prevention of MS relapse (e.g., interferon, natalizumab, glatiramer acetate, fingolimod, teriflunomide or dimethyl fumarate) within 6 months prior to baseline.
4. Any previous treatment with anti-CD4, cladribine, cyclophosphamide or mitoxantrone within 2 years prior to baseline.
5. Treatment with any investigational agent within 3 months prior to baseline.

Exclusions for General Safety:

6. Pregnancy or lactation.
7. For patients of reproductive potential, a positive result from a serum pregnancy test at screening, or not willing to use reliable means of contraception (physical barrier [patient or partner] in conjunction with a spermicidal product, contraceptive pill, patch, injectables, intrauterine device or intrauterine system) during the treatment period and for at least 3 months after the last dose of study drug.
8. Any surgical procedure (except for minor surgeries) within 4 weeks prior to baseline.
9. Evidence of other demyelinating disease or progressive multifocal leukoencephalopathy (PML).
10. Evidence of serious uncontrolled concomitant diseases that may preclude patient participation, as described; other nervous system disease, cardiovascular disease, hematologic/hematopoiesis disease, respiratory disease, muscular disease, endocrine disease, renal/urologic disease, digestive system disease, congenital or acquired severe immunodeficiency.
11. Known active infection (excluding fungal infections of nail beds or caries dentium) within 4 weeks prior to baseline.
12. Evidence of chronic active hepatitis B or C.
13. History of drug or alcohol abuse within 1 year prior to baseline.
14. History of diverticulitis that, in the Investigator's opinion, may lead to increased risk of complications such as lower gastrointestinal perforation.
15. Evidence of active tuberculosis (TB) (excluding patients receiving chemoprophylaxis for latent TB infection).
16. Evidence of active interstitial lung disease.
17. Receipt of any live or live attenuated vaccine within 6 weeks prior to baseline.
18. History of malignancy within the last 5 years, including solid tumors, hematologic malignancies and in situ carcinoma (except basal cell and squamous cell carcinomas of the skin, or in situ carcinoma of the cervix uteri that have been completely excised and cured).
19. History of severe allergic reaction to a biologic agent (e.g., shock, anaphylactic reactions).
20. Active suicidal ideation within 6 months prior to screening, or history of suicide attempt within 3 years prior to screening.
21. History of Stevens-Johnson syndrome (SJS).

Laboratory exclusion criteria (at screening):

22. Following laboratory abnormalities at screening*.
 - a. White blood cells (WBC) $< 3.0 \times 10^3/\mu\text{L}$
 - b. Absolute neutrophil count (ANC) $< 2.0 \times 10^3/\mu\text{L}$
 - c. Absolute lymphocyte count $< 0.5 \times 10^3/\mu\text{L}$
 - d. Platelet count $< 10 \times 10^4/\mu\text{L}$
 - e. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 times the upper limit of normal (ULN).

* If retest is conducted, the last value of retest before randomization must meet study criteria.

Concomitant Medications

Permitted

Treatment of Relapses: At the time of a relapse, treatment with Intravenous corticosteroids, intravenous immunoglobulin and/or plasma exchange or plasmapheresis was permitted.

Symptomatic Treatment: Stable doses of medications to treat pain were permitted

Prohibited

Prior to and during the study

IL-6 therapy (tocilizumab), alemtuzumab, total body irradiation, bone marrow transplant

Within 2 years of baseline and during the study

Anti-CD4 therapies, cladribine, cyclophosphamide, mitoxantrone

Within 6 months of baseline and during the study

Eculizumab, anti-BLyS monoclonal antibody (e.g., belimumab), anti-CD20 treatment (e.g., rituximab, ocrelizumab, ofatumumab), any other treatment for prevention of MS relapse (e.g., interferon, natalizumab, glatiramer acetate, fingolimod, teriflunomide, dimethyl fumarate)

Within 3 months of baseline and during the study

Treatment with any investigational agent

Within 6 weeks of baseline and during the study

Immunization with live or live attenuated vaccine

From baseline to the end of the study

Immunosuppressants (e.g., azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, tacrolimus)

Corticosteroid, IVIG except for rescue therapy for clinical relapse

Treatment

Results from a phase 1 single-dose study in healthy subjects and a multiple dose study in patients with rheumatoid arthritis showed that satralizumab-mwge 120 mg Q4W inhibited IL-6 signaling completely, whereas lower doses (30, 60 mg Q4W) did not.

Relapse Identification

During the screening period patients were trained on the possible symptoms and signs of a relapse of optic neuritis or myelitis, or a relapse involving other locations. All reports of potential relapses from patients regardless of the time of the report was described in the

Relapse Assessment Form. During the double-blind period, the site was to contact each subject weekly by phone calls between the scheduled site visits, to query any change in symptoms or other signs of a potential relapse. If a subject became aware of signs or symptoms which might indicate relapse, the patient was to return to the site for an extra visit as soon as possible with a target date set for no more than three days after reporting the symptoms to the site. The examining Investigator was to perform an EDSS/FSS assessment within 7 days after the patient reports the symptoms to the site.

Each extra visit following relapse was to be captured in the electronic case report form (eCRF) and a separate Relapse Assessment Form was to be completed by the site and sent with the accompanying necessary data, to (b) (4) immediately regardless of the assessment of the site staff as to whether a potential relapse met protocol-defined relapse and regardless of the time when EDSS/FSS assessment was performed. During the double-blind period, the form and the data will be reviewed by the Clinical Events Committee (CEC). 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 protocol definition of a relapse. In order to ensure that no relapse events were missed by the Investigator, the adjudication process included a concurrent review of all cases for potential relapses that may have been missed. A relapse which was regarded as a protocol-defined relapse by the CEC followed by confirmation that the EDSS/FSS assessment was performed within seven days after the patient reported the symptoms to the site, was treated as an event for purposes of the primary efficacy analysis.

The clinical criteria for a new or worsened neurologic deficit were:

- An increase of at least 1.0 point on the EDSS score excepting increase to 1.0 or 1.5 from zero (i.e., a 2.0-point increase on the EDSS is required if the baseline was zero)
- An increase of at least 2.0 points on one of the appropriate 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

Study Endpoints

The primary efficacy variable is the time to first protocol-defined relapse (TFR) based on adjudication by the CEC evaluations. TFR is defined as the time from the date of randomization until the first occurrence of a relapse (day of onset as reported by the investigator) throughout the double-blind period.

The key secondary endpoints are:

- Analysis of change in Visual Analogue Score (VAS) for pain score from baseline to week 24 using Analysis of Covariance (ANCOVA) (Baseline Observation Carried Forward (BOCF)).
- Analysis of change in Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale score from baseline to week 24 using ANCOVA (BOCF).

Statistical Analysis Plan (SAP)

Version 7 (final)

The primary efficacy analysis as defined in the final SAP is adjusted for the following baseline covariates:

- Prior therapy for prevention of NMO/NMOSD attack (B-cell depleting therapy or immunosuppressants/others)
- Most recent attack in the last one year prior to screening (first attack or relapse).

The primary efficacy endpoint is TFR based on protocol-defined relapses confirmed by the CEC with EDSS/FSS assessment performed by the examining assessor within 7 days after relapse symptoms were reported to the site by the subject. TFR is defined as the time from the date of the randomization until the first occurrence of relapse throughout the double-blind period. Time point of relapse onset is defined as time at which the subject experiences any new or worsening neurological NMO/NMOSD symptoms representing clinical relapse(s) which is later confirmed by the CEC as protocol-defined. Patients are censored at the end of double-blind period for efficacy analysis. A stratified log-rank test using strata of prior therapy for prevention of NMO/NMOSD attack (B-cell depleting therapy or immunosuppressants/others) and the most recent attack in the last year prior to baseline (first attack or relapse) are used. The Kaplan-Meier method is used to estimate the TFR based on protocol-defined relapse distribution for each treatment group. Estimates of the treatment effect is expressed as the hazard ratio and 95% confidence intervals using a Cox proportional-hazards model. The model is stratified by prior therapy for prevention of NMO/NMOSD attack (B-cell depleting therapy or immunosuppressants/others) and the most recent attack in the last one year prior to screening (first attack or relapse).

Additionally, sensitivity analyses of TFR (protocol-defined relapse) using a weighted stratified log-rank test, TFR (clinical relapse), TFR (treated clinical relapse), TFR (treated clinical relapse: optic neuritis), and protocol-defined relapse based on CEC adjudication (regardless of assessment limit of 7 days) were conducted for the ITT.

Clinical relapses: All relapses reported by investigators are handled as events for TFR.

Treated clinical relapses: Relapses treated with rescue therapy are handled as events.

Treated clinical relapse: optic neuritis: Relapses treated with rescue therapy and judged as

optic neuritis by the investigator are handled as events

The primary and 2 key secondary efficacy endpoints are analyzed in hierarchical order, beginning with the TFR based on protocol-defined relapses, followed by the VAS for pain, and ending with FACIT fatigue. A fixed-sequence approach is applied to control the overall significance level at 0.05.

The intent-to-treat (ITT) population consists of all randomized subjects and serves as the primary population for the analysis of efficacy. The All-Subjects-Treated (all satralizumab-mwge) population is defined as all enrolled subjects who took at least one dose of active study drug at any time.

Baseline is defined as the latest date before or on the date prior to first administration with either placebo or satralizumab-mwge.

The duration of double-blind period was defined from the day of the randomization to the earliest day of 1) clinical cutoff date (CCOD), 2) the day before the first treatment in the extension period, 3) the end of the study, or 4) last contact for patients lost to follow up.

Amendments to the SAP

Amendment from Ver 1.0 to 2.0

For TFR, the condition of handling missing data has been added. For patients with protocol-defined relapse based on CEC evaluation, but not performed EDSS/FSS assessment within seven days after the patient reports the symptoms to the site, the TFR will be censored on the date of relapse onset. The sensitivity analysis of protocol-defined relapse based on CEC adjudication has also been added.

Amendment from Ver 2.0 to 3.0

The primary purpose of this SAP amendment was to address FDA comments. For primary endpoint, analysis method was changed to the log-rank based permutation test from stratified log-rank test. For key secondary endpoints of VAS and FACIT, ANCOVA has been added for change from baseline at 24 weeks.

Amendment from Ver 3.0 to 4.0

The definition of censoring was revised.

Amendment from Ver 4.0 to 5.0

The assumption for determination of sample size has been revised.

Amendment from Ver 5.0 to 6.0

FDA Response dated 28th March 2017 for type C meeting Question 7:

We agree that an asymptotic log-rank test instead of a permutation-based log-rank test can be used as the primary analysis method. You may keep the permutation-based log-rank test as a secondary analysis method.

Another purpose is to revise the context to align with the amended protocol version 7.0 dated 13th July 2017. The following changes are made in this Statistical Analysis Plan (SAP) from the previous version of SAP due to the amendment to the protocol.

- For primary endpoint, analysis method has changed to stratified log-rank test from the log-rank based permutation test.
- Only treatment-emergent adverse events are collected in this study. Previously the SAP contained summaries of adverse events and treatment-emergent adverse events, the latter were removed to avoid redundancy.
- Detailed description on the identification of the following adverse event were added: serious infections, opportunistic infections, anaphylaxis, injection related reactions and injection site reactions.
- Detailed description of the following efficacy evaluation is added: EQ-5D Scoring and Visual acuity function.
- Detailed description of the immunogenicity and immunogenicity analyses were added.
- The analysis of relapse-free subjects using logistic regression will not be conducted because of a lot of early events.
- Clarify the definition of baseline ARR.
- Resolve inconsistencies mainly for scope of analysis in SAP.

Amendment from Ver 6.1 to 7.0

The primary purpose of this SAP amendment is to include additional sensitivity analyses for the primary and key secondary endpoints:

- Sensitivity analysis for primary endpoint TFR (protocol-defined relapse) using stratified weighted log-rank test with Fleming-Harrington weight function was added.
- Sensitivity analysis for change from baseline in pain and fatigue was added, including additional information from the withdrawal and OLE baseline visits.

Protocol Amendments

There were seven protocol amendments to the original Protocol SA-309 JG approved on 14 Nov 2013. The first patient was enrolled into the study on 05 Aug 2014, and therefore, no patients were enrolled under Protocol version 1.

Protocol 2.0 (dated 18 Feb 2014)

- Prohibition of concomitant immunosuppressants and corticosteroid (except for rescue therapy) use after baseline.
- Removal of run-in period where oral corticosteroids were given.
- Randomization stratified by type of prior treatment (B-cell depleting therapy or immunosuppressants vs others) and most recent attack in the year prior to randomization (first attack vs relapse) instead of baseline ARR and geographic region. These stratification factors were also included in any stratified analyses

Protocol 3.0 (dated 26 May 2014)

- Change in MRI findings removed from criteria for PDR as suggested by FDA. Therefore, MRI scans are from then on optional and require a separate signature on the informed consent
- An iDMC futility analysis was not to be conducted.
- A time limit of relapse evaluation (within 7 days of relapse) is added to the definition of PDR.
- Starting date for time to first relapse was based on randomization date instead of first study treatment administration, as suggested by FDA.

Protocol 4.0 (dated 02 Sep 2014)

- For PDR assessment, specifications of increases in EDSS and FSS when the scores were 0 at baseline were added, as suggested by FDA.
- Censoring rule for PDRs without an assessment of EDSS within 7 days added. The TFR was to be censored on the date of relapse onset in these cases.
- Sensitivity analyses were added for the primary endpoint.

Protocol 5.0 (dated 05 Nov 2015)

Based on FDA comments, it was clarified that only patients who have a PDR confirmed by the CEC, can enter the extension period. This was done to minimize dropouts from the double-blind period. The censoring rules were also adjusted to reflect this change.

As per recommendation from FDA, the statistical method for primary analysis was changed from stratified two-sided log-rank test to log-rank based permutation test.

Protocol 6.0 (dated 01 Mar 2016)

The sample size was increased from 70 to 90 patients and the total number of CEC confirmed PDRs needed for primary analysis was increased from 19 to 44. These changes also led to a longer expected study duration (38 months instead of 27). The hazard ratio of satralizumab-mwge over placebo was modified considering the mechanism of action of satralizumab-mwge. The hazard ratio (satralizumab-

mwge to placebo) is assumed to be 1.0 during the initial 2 months. The assumption that the hazard ratio is 0.25 after the initial 2 months was not changed. Additionally, the estimated post-baseline ARR in the placebo group was updated from 0.4 to 1.35 based on a publication.

Protocol 7.0 (dated 13 Jul 2017)

Implementation of satralizumab-mwge (SA237) prefilled syringe (PFS) with needle safety device (NSD). PFS can be used in the extension phase.

Protocol 8.0 (dated 14 Jun 2018)

- The end of double-blind period was updated to prevent prolonged exposure to an unknown risk-benefit balance drug. The definition of the end of the double-blind period was changed to include a maximal duration completion of 1.5 years after the date of the last patient randomized, if the target number of CEC confirmed PDRs (44) has not been reached.
- The analysis method for the primary endpoint was changed as per agreement between the sponsor and FDA. A stratified log-rank test is used instead of a log-rank test-based permutation test. The change was proposed by the Sponsor
- Analyses of key secondary endpoints and sensitivity analyses were clarified.

Changes to Planned Analyses

- The analysis of the T25W was changed from time to speed (1/time), since the value on the time scale did not meet the normality assumption of the mixed-model that was used for the analysis.
- PK data are reported in a separate Population PK report.
- IRRs and ISRs were recorded in multiple ways in the eCRF. Therefore, the definitions were clarified (Section 3.9.7.5).
- Due to sensitivity issues (Section 3.9.8), neutralizing antibody assay results were not considered reliable and are not reported.
- Subgroup analysis based on AQP4 status (positive vs. negative) is presented.
- ADA subgroup analysis was not performed due to small patient numbers and assay sensitivity issues.
- Due to small subgroup sample size, subgroup analyses of safety data are not presented in this report and will be conducted on pooled populations across studies.

Version 8 to version 9

Week 96 is no longer the last administration of satralizumab-mwge. Patients can continue to receive open-label treatment with satralizumab-mwge until commercial availability, the availability of satralizumab-mwge as post-trial access in accordance with local regulation, or until the Sponsor decides to discontinue the development program

6.1.2. Study Results

Compliance with Good Clinical Practices

The sponsor reports that this study was conducted in accordance with the Declaration of Helsinki and the International Council on Harmonization principles of Good Clinical Practice.

Financial Disclosure

The sponsor received a financial disclosure statement from 414 of 415 investigators. Two investigators reported a disclosable financial interest, both from the same site (b) (6) which enrolled (b) (6) subjects. The primary endpoint analysis result is not affected by removal of these (b) (6) subjects.

Patient Disposition

Informed consent was obtained from 95 patients, and 95 patients were enrolled and randomized. The first patient was enrolled on August 5, 2014 and the last patient enrolled completed 1.5 years of treatment on October 12, 2018, which is the Clinical Cut-off Date (CCOD). The database was locked on December 4, 2018. All randomized subjects had a least one dose of study treatment and are included in the Intent to Treat (ITT) and in the Safety databases. The intended treatment for the randomized double-blinded phase of the trial was the same as the actual treatment for all subjects.

Eligible patients were randomized at 44 sites in 13 countries. Approximately 60% of those randomized were from the US and Canada (Table 2).

Table 2: Randomization by country, Study 309JG

Country	PLACEBO	SA237	Subjects(filtered)
USA	13 (40.6%)	34 (54.0%)	47 (49.5%)
CAN	3 (9.4%)	8 (12.7%)	11 (11.6%)
UKR	3 (9.4%)	7 (11.1%)	10 (10.5%)
POL	3 (9.4%)	5 (7.9%)	8 (8.4%)
KOR	1 (3.1%)	4 (6.3%)	5 (5.3%)
TWN	3 (9.4%)	1 (1.6%)	4 (4.2%)
BGR	3 (9.4%)	1 (1.6%)	4 (4.2%)
GEO	1 (3.1%)	0 (0.0%)	1 (1.1%)
TUR	1 (3.1%)	0 (0.0%)	1 (1.1%)
MYS	1 (3.1%)	0 (0.0%)	1 (1.1%)
HRV	0 (0.0%)	1 (1.6%)	1 (1.1%)
ITA	0 (0.0%)	1 (1.6%)	1 (1.1%)
ROU	0 (0.0%)	1 (1.6%)	1 (1.1%)
Subjects(filtered)	32 (100.0%)	63 (100.0%)	95 (100.0%)

Country	PLACEBO	SA237	Subjects(filtered)
1stColItemSubjects	32 (100.0%)	63 (100.0%)	(Denom=1stColTot)

Source: JRev309SelADSLITTFL_Y COUNTRYbyTRT01P

One site randomized 8 patients, one randomized 7, two sites randomized 5 patients, and 4 sites randomized 4 patients each. These 8 sites accounted for 18.2% of the patients randomized. Approximately 75% of sites randomized one or two patients each ([Table 3](#)).

Table 3: Number of patients randomized by number of sites

RANDOMIZED	SITEID	
n	n	%
1	22	50.0%
2	10	22.7%
3	4	9.1%
4	4	9.1%
5	2	4.5%
7	1	2.3%
8	1	2.3%
Total sites	44	100.0%

Source: ADSL 309 By (SITEID) By (N Rows)

The 8 sites with the highest number of patients randomized, shaded in [Table 4](#) below, accounted for 25% of the confirmed relapses in the placebo group and 48% of the confirmed relapses in the group treated with satralizumab-mwge.

Reviewer Comment: The highest enrolling sites did not appear to influence the primary outcome result in favor of satralizumab-mwge.

Table 4: CEC confirmed relapses by site, highest 11 enrolling sites, by treatment group, ITT

SITEID	Yes, PLACEBO		Yes, SA237	
	N	%	N	%
2002	1	6.3%	4	19.0%
8302	1	6.3%	1	4.8%
2519	0	0.0%	1	4.8%
2521	0	0.0%	2	9.5%
2532	0	0.0%	1	4.8%
4403	1	6.3%	0	0.0%
2001	1	6.3%	0	0.0%

SITEID	Yes, PLACEBO		Yes, SA237	
	N	%	N	%
2515	0	0.0%	1	4.8%
2520	1	6.3%	1	4.8%
2528	0	0.0%	2	9.5%
7508	1	6.3%	1	4.8%
Top 8	4	25%	10	48%
Total Confirmed Relapses	16	100%	21	100%

Source: ADRLP 309 PDRCECFL by TRT01P By (SITEID)

Sixty-three (63) patients were randomized to treatment with satralizumab-mwge and 32 to placebo.

Placebo

Of the 32 patients randomized to placebo, 17 had a clinical relapse (16 of which were confirmed) and all 17 entered the Open-Label Extension (OLE). Four subjects withdrew during the RCP without having a relapse; 11 subjects were continuing in the double-blind phase at the CCOD. Twenty-seven (27) were considered to have completed the double-blind phase, 4 discontinued, and 1 was ongoing at the time of the clinical cut-off date.

Satralizumab-mwge

Of the 63 subjects randomized to satralizumab-mwge, 49 (77.8%) were considered to have completed the RCP. Seven (11.1%) discontinued the trial for reasons other than a relapse and 7 were considered ongoing at the time of CCOD ([Table 5](#)). Of the 63 patients randomized to treatment with satralizumab-mwge, 21 had a clinical relapse (31 clinical relapses but 21 confirmed relapses). Of the 21 with a confirmed relapse, 18 entered the OLE. The disposition of subjects who were anti-AQP4 IgG seropositive is listed in [Table 6](#).

Table 5: Disposition of subjects in the Double-Blind Treatment Phase; ITT, Study 309

End of Treatment status RCP (EOT01STT)	Reported Reason Discontinuation from RCP (DCP01RS)	PLACEBO	SA237
Completed		27 (84.4%)	49 (77.8%)
Discontinued	ADVERSE EVENT	1 (3.1%)	1 (1.6%)
	NON-COMPLIANCE WITH STUDY DRUG	0 (0.0%)	1 (1.6%)
	OTHER	1 (3.1%)	3 (4.8%)
	WITHDRAWAL BY SUBJECT	2 (6.3%)	2 (3.2%)
Ongoing	(missing)	1 (3.1%)	7 (11.1%)
Total	Subjects(filtered)	32 (100.0%)	63 (100.0%)
Total	1stColltemSubjects	32 (100.0%)	63 (100.0%)

Source: JRev309SelITTF_L_Y EOT01STTbyDCP01RSbyTRT01p

Table 6: Disposition of subjects in the RCP, anti-AQP4 seropositive adults, study 309

End of Treatment status RCP (EOT01STT)	Reported Reason Discontinuation from RCP DCP01RS	PLACEBO	SA237
Completed		20 (87.0%)	33 (80.5%)
Discontinued	ADVERSE EVENT	1 (4.3%)	0 (0.0%)
	NON-COMPLIANCE WITH STUDY DRUG	0 (0.0%)	1 (2.4%)
	OTHER	0 (0.0%)	2 (4.9%)
	WITHDRAWAL BY SUBJECT	1 (4.3%)	2 (4.9%)
Ongoing	(missing)	1 (4.3%)	3 (7.3%)
Total	Subjects(filtered)	23 (100.0%)	41 (100.0%)
Total	1stColItemSubjects	23 (100.0%)	41 (100.0%)

Source: JRev309SelITTFI_Y AQP4J_SEROPOS EOT01STTbyDCP01RSbyTRT01P

Protocol Violations/Deviations

At least one major protocol deviation occurred in approximately 60% of subjects in both treatment groups (Table 7). Of those considered major, the most common involved either tests and procedures or administration of investigational product (IP). None of the deviations involving procedures or tests resulted in exclusion of a subject from the primary analyses. Nearly all deviations involving IP administration involved administration at the time of an active infections. There were 18 in the placebo group and 20 in the satralizumab-mwge group.

Table 7: Protocol violations or deviations by category and treatment group, study 309.

Category for Protocol Deviation	PLACEBO	SA237	Subjects(filtered)
MAJOR	20 (64.5%)	37 (60.7%)	57 (60.0%)
MINOR	31 (100.0%)	60 (98.4%)	91 (95.8%)
Subjects(filtered)	31 (100.0%)	61 (100.0%)	95 (100.0%)
1stColItemSubjects	31 (100.0%)	61 (100.0%)	(Denom=1stColTot)

Source: JRevSelADSLRANDFL_Y DVCATbyTRT01P

Table of Demographic Characteristics

Table 8 Reviewer Comment: The imbalances noted are probably attributable to chance and the small size of the trial. It is not likely that these affect the key analyses but subgroup analyses for the key differences are included in the appropriate efficacy and safety sections of this review.

Table 8: Demographic characteristics, ITT, study 309

Subgroup	PLACEBO (N = 32) n (%)	SA237 (N = 63) n (%)	Total (N = 95) n (%)
Sex			
Female	31 (96.9)	46 (73.0)	77 (81.1)
Male	1 (3.1)	17 (27.0)	18 (18.9)
Age			
Mean	40.47	45.35	43.71
Standard Deviation	10.45	12.05	11.71
Minimum	20	21	20
Median	42.5	46	45
Maximum	56	70	70
Age Group			
AGE < 40	13 (40.6)	18 (28.6)	31 (32.6)
40 <= AGE	19 (59.4)	45 (71.4)	64 (67.4)
Race			
American Indian or Alaska Native	0 (0.0)	2 (3.2)	2 (2.1)
Asian	6 (18.8)	8 (12.7)	14 (14.7)
Black or African American	3 (9.4)	13 (20.6)	16 (16.8)
Other	1 (3.1)	3 (4.8)	4 (4.2)
White	22 (68.8)	37 (58.7)	59 (62.1)
Ethnicity			
Hispanic or Latino	3 (9.4)	9 (14.3)	12 (12.6)
Missing	1 (3.1)	4 (6.3)	5 (5.3)
Not Hispanic or Latino	28 (87.5)	50 (79.4)	78 (82.1)
Region			
Asia	7 (21.9)	5 (7.9)	12 (12.6)
Canada	3 (9.4)	8 (12.7)	11 (11.6)
Europe	9 (28.1)	16 (25.4)	25 (26.3)
United States	13 (40.6)	34 (54.0)	47 (49.5)

Source: JMPClinical DEM_TOOL

The demographics for the population of adults who were anti-AQP4 IgG seropositive are listed in [Table 9](#). The differences between the treatment groups are similar to those for the full ITT.

Table 9: Demographics, anti-AQP4 IgG seropositive, study 309

Subgroup	PLACEBO (N = 23) n (%)	SA237 (N = 41) n (%)	Total (N = 64) n (%)
Sex			
Female	22 (95.7)	31 (75.6)	53 (82.8)
Male	1 (4.3)	10 (24.4)	11 (17.2)
Age			
Mean	40.13	46.05	43.92
Standard Deviation	11.52	12	12.08
Minimum	20	22	20
Median	43	47	45
Maximum	56	70	70
Age Group			
Age Group 1 (AGE < 40)	10 (43.5)	12 (29.3)	22 (34.4)
Age Group 2 (40 <= AGE)	13 (56.5)	29 (70.7)	42 (65.6)
Race			
American Indian or Alaska Native	0 (0.0)	2 (4.9)	2 (3.1)
Asian	6 (26.1)	7 (17.1)	13 (20.3)
Black or African American	3 (13.0)	11 (26.8)	14 (21.9)
Other	1 (4.3)	2 (4.9)	3 (4.7)
White	13 (56.5)	19 (46.3)	32 (50.0)
Ethnicity			
Hispanic or Latino	3 (13.0)	7 (17.1)	10 (15.6)
Missing	0 (0.0)	4 (9.8)	4 (6.2)
Not Hispanic or Latino	20 (87.0)	30 (73.2)	50 (78.1)
Region			
Asia	6 (26.1)	5 (12.2)	11 (17.2)
Canada	2 (8.7)	4 (9.8)	6 (9.4)
Europe	5 (21.7)	8 (19.5)	13 (20.3)
United States	10 (43.5)	24 (58.5)	34 (53.1)

Source: DM_TOOL AQP4pos adults

Medical History

The most common concurrent medical conditions at baseline are listed in [Table 10](#). There was an imbalance for some disorders such as drug hypersensitivity and depression, most likely

attributable to the small size of the trial. It is unlikely that these affected the key outcome measures or safety results.

Table 10: Concurrent medical conditions by standardized term, most common, Study 309

MHDECOD	PLACEBO		SA237	
	N	%	N	%
Hypertension	5	15.6%	17	27.0%
Drug hypersensitivity	14	43.8%	6	9.5%
Depression	3	9.4%	15	23.8%
Gastroesophageal reflux disease	2	6.3%	15	23.8%
Constipation	2	6.3%	9	14.3%
Hyperlipidaemia	1	3.1%	6	9.5%
Anaemia	2	6.3%	4	6.3%
Anxiety	2	6.3%	4	6.3%
Hypercholesterolaemia	3	9.4%	3	4.8%
Hypothyroidism	3	9.4%	3	4.8%
Insomnia	2	6.3%	4	6.3%
Systemic lupus erythematosus	3	9.4%	3	4.8%
Urinary tract infection	3	9.4%	3	4.8%
Vitamin D deficiency	2	6.3%	4	6.3%
Asthma	1	3.1%	4	6.3%
Back pain	1	3.1%	4	6.3%
Headache	2	6.3%	3	4.8%
Muscle spasms	1	3.1%	4	6.3%
Neuralgia	2	6.3%	3	4.8%
Neurogenic bladder	1	3.1%	4	6.3%
Paraesthesia	1	3.1%	4	6.3%
Seasonal allergy	2	6.3%	3	4.8%
Sjogren's syndrome	2	6.3%	3	4.8%

Source: ATIREL_CONCOM Subset of MHCAT_MEDHX Subset of ADMH 309JG TRT01P By (MHDECOD)

*: percent of randomized

The incidence of prior and concurrent diseases in the musculoskeletal MHSOC are shown in [Table 11](#). Six subjects in the placebo group (18.8%) and 8 (12.7%) in the satralizumab-mwge group had a history of possible autoimmune disorders other than NMOSD.

Table 11: Musculoskeletal and connective tissue disorders, prior and concurrent, Study 309

MHDECOD	PLACEBO		SA237	
	N	N	%*	N
Systemic lupus erythematosus	3	9.4%	3	4.8%
Back pain	1	3.1%	4	6.3%
Muscle spasms	1	3.1%	4	6.3%
Sjogren's syndrome	2	6.3%	3	4.8%
Osteoporosis	0	0.0%	4	6.3%
Arthralgia	1	3.1%	2	3.2%
Arthritis	0	0.0%	3	4.8%
Intervertebral disc protrusion	2	6.3%	1	1.6%
Myalgia	2	6.3%	1	1.6%
Pain in extremity	0	0.0%	3	4.8%
Muscular weakness	1	3.1%	1	1.6%
Neck pain	2	6.3%	0	0.0%
Osteonecrosis	0	0.0%	2	3.2%
Rheumatoid arthritis	0	0.0%	2	3.2%
Bursitis	0	0.0%	1	1.6%
Foot deformity	0	0.0%	1	1.6%
Joint stiffness	1	3.1%	0	0.0%
Myofascial pain syndrome	0	0.0%	1	1.6%
Osteoarthritis	1	3.1%	0	0.0%
Osteopenia	0	0.0%	1	1.6%
Psoriatic arthropathy	1	3.1%	0	0.0%
Scoliosis	0	0.0%	1	1.6%
Spinal osteoarthritis	0	0.0%	1	1.6%
Spondylolisthesis	0	0.0%	1	1.6%
Trigger finger	0	0.0%	1	1.6%

Source: MHSOC_MUSCSKEL Subset of MHCAT_MEDHX Subset of ADMH 309JG TRT01P By (MHDECOD)

*: percent of randomized

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline Disease Characteristics

The characteristics of NMOSD at baseline are listed in [Table 12](#) for the ITT and for the anti-AQP4 IgG seropositive population in [Table 13](#). The trial was generally well balanced by treatment group for these characteristics. Approximately 70% of subjects were seropositive for the anti-AQP4-IgG antibody. For nearly all subjects, the qualifying attack in the year prior to enrollment was not the first attack. The median EDSS score was 3.5 for the placebo group and 4

for the satralizumab-mwge group. See Appendix 13.5 for the full EDSS scale.

Reviewer Comment: In response to an Additional Information Request, the sponsor confirmed that the method used for screening patients for the presence of the anti-AQP4 antibody was the Kronus Aquaporin-4 Autoantibody (AQP4Ab) ELISA assay. This test has been cleared by the Center for Devices and Radiological Health (CDRH). The link to the clearance is below. The overall sensitivity for NMO, NMOSD, and NMO+NMOSD was 81.2%, 48.1%, and 68.6% respectively. The specificity was 98.1% for all three.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?ID=DEN150030>

Table 12: Baseline Disease Characteristics, ITT, Study 309

Characteristic	Placebo		SA237	
	n	%	N	%
AQP4-IgG status at baseline				
Positive	23	71.9	41	65.1
NMO diagnosis				
NMO	24	75.0	47	74.6
NMOSD	8	25.0	16	25.4
Attack in previous year				
First attack	4	12.5	7	11.1
Relapse	28	87.5	56	88.9
Previous therapy				
B-cell depleting	4	12.5	8	12.7
Immunosuppressants/other	28	87.5	55	87.3
Baseline EDSS				
Mean $\pm$ SD	3.7 $\pm$ 1.6		3.9 $\pm$ 1.5	
Median	3.5		4.0	
Min, Max	1.0, 6.5		1.5, 6.5	

Source: ADSL 309.jmp

Table 13: Baseline Disease Characteristics, anti-AQP4 IgG seropositive population, Study 309

Characteristic	Placebo		SA237	
	n	%	N	%
NMO diagnosis				
NMO	15	65.2	26	63.4
NMOSD	8	34.8	15	36.6
Attack in previous year				
First attack	4	17.4	5	12.2
Relapse	19	82.6	36	87.8
Previous therapy				
B-cell depleting	4	17.4	5	12.2
Immunosuppressants/other	19	82.6	36	87.8

Characteristic	Placebo		SA237	
	n	%	N	%
Baseline EDSS				
Mean ±SD	3.4±1.6		4.0±1.5	
Median	3.5		4.0	
Min, Max	1, 6.5		1.5, 6.5	

Source: AQP4J_SEROPOS Subset of ADL 309 Ir

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Compliance was calculated according to the SAP as the number of SC injections during the RCP divided by the number of planned SC injections during the RCP times 100%. The median compliance was essentially 100% for both treatment groups ([Table 14](#)). Two placebo and two satralizumab-mwge subjects had a compliance rate under 90%.

Table 14: Treatment compliance, ITT, study 309

TRT01P	Compliance*					
	N Rows	Mean	Std Dev	Min	Max	Median
PLACEBO	32	110	34.9	76.9	200	99.8
SA237	63	97.7	6.28	64.4	102	99.9

Source: Join ADL309Ir with SUM NDOSE by USUBJID Compliance By (TRT01P).jmp

*: number of doses/number of expected doses ((Treatment duration/28) +2 if duration ≥15; else = 1) X 100

Concurrent medications during the RCP

The categories of medications being taken during the RCP are listed in [Table 15](#). The most common specific medications are listed in [Table 16](#).

Table 15: Categories of concomitant medications during the RCP, ATC1, study 309

ATC Level 1 Text	PLACEBO	SA237
NERVOUS SYSTEM	18 (56.3%)	31 (49.2%)
ANTIINFECTIVES FOR SYSTEMIC USE	13 (40.6%)	31 (49.2%)
ALIMENTARY TRACT AND METABOLISM	13 (40.6%)	24 (38.1%)
RESPIRATORY SYSTEM	12 (37.5%)	23 (36.5%)
MUSCULO-SKELETAL SYSTEM	8 (25.0%)	25 (39.7%)
BLOOD AND BLOOD FORMING ORGANS	5 (15.6%)	16 (25.4%)
SYSTEMIC HORMONAL PREPS, EXCL. SEX HORMONES AND INSULINS	5 (15.6%)	11 (17.5%)
VARIOUS	6 (18.8%)	9 (14.3%)
DERMATOLOGICALS	5 (15.6%)	10 (15.9%)
CARDIOVASCULAR SYSTEM	1 (3.1%)	13 (20.6%)
GENITO URINARY SYSTEM AND SEX HORMONES	4 (12.5%)	10 (15.9%)
SENSORY ORGANS	3 (9.4%)	7 (11.1%)

ATC Level 1 Text	PLACEBO	SA237
ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS	0 (0.0%)	2 (3.2%)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	0 (0.0%)	1 (1.6%)
Subjects(filtered)	23 (71.9%)	54 (85.7%)
1stColItemSubjects	32 (100.0%)	63 (100.0%)

Source: JRevSelADSLITFL_Y ATC1byTRT01PfiltCMCAT_OTHER EPOCH_RCP

Table 16: Most common concomitant medications during the RCP, study 309

Standardized Medication Name	PLACEBO	SA237	Subjects(filtered)
PARACETAMOL	7 (21.9%)	14 (22.2%)	21 (22.1%)
IBUPROFEN	2 (6.3%)	11 (17.5%)	13 (13.7%)
CIPROFLOXACIN	4 (12.5%)	7 (11.1%)	11 (11.6%)
NITROFURANTOIN	5 (15.6%)	6 (9.5%)	11 (11.6%)
DIPHENHYDRAMINE HYDROCHLORIDE	4 (12.5%)	6 (9.5%)	10 (10.5%)
AMOXICILLIN	2 (6.3%)	7 (11.1%)	9 (9.5%)
METHYLPREDNISOLONE	2 (6.3%)	6 (9.5%)	8 (8.4%)
INFLUENZA VACCINE	0 (0.0%)	7 (11.1%)	7 (7.4%)
GABAPENTIN	1 (3.1%)	6 (9.5%)	7 (7.4%)
CEFALEXIN	2 (6.3%)	5 (7.9%)	7 (7.4%)
Subjects(filtered)	23 (71.9%)	54 (85.7%)	95 (100.0%)
1stColItemSubjects	32 (100.0%)	63 (100.0%)	(Denom=1stColTot)

Source: JRevSelADSLITFL_Y CMDECOBdyTRT01PfiltCMCAT_OTHER EPOCH_RCP

The use of medications for treatment of a relapse, i.e. “rescue treatment”, during the RCP is listed in [Table 17](#). Rescue treatment was nearly always administered intravenously.

Table 17: Rescue treatment for relapses during the RCP, study 309

Standardized Medication Name	PLACEBO	SA237
Methylprednisolone	8 (25.0%)	10 (15.9%)
Methylprednisolone Sodium Succinate	6 (18.8%)	12 (19.0%)
Prednisone	2 (6.3%)	2 (3.2%)
Dexamethasone	2 (6.3%)	0 (0.0%)
Plasma	0 (0.0%)	2 (3.2%)
Prednisolone	1 (3.1%)	0 (0.0%)
No Ingredients Specified	1 (3.1%)	0 (0.0%)
Camphor,Menthol,Methyl Salicylate	1 (3.1%)	0 (0.0%)
Cyclophosphamide	0 (0.0%)	1 (1.6%)
Metoclopramide	0 (0.0%)	1 (1.6%)
Benfotiamine,Cyanocobalamin,Pyridoxine Hydrochloride	1 (3.1%)	0 (0.0%)
Subjects (Filtered)	17 (53.1%)	21 (33.3%)
1stcolitemsubjects	32 (100.0%)	63 (100.0%)

Source: JRevSelADSLITFL_Y CMDECOBdyTRT01PfiltCMCAT_NMO INDIC_RESCUE EPOCH_RCP

The start of rescue treatment with IV corticosteroids in study days for was considerably later for those treated with satralizumab-mwge ([Table 18](#)).

Table 18: Study day start of IV corticosteroid rescue therapy, earliest use, study 309

TRT01P	Earliest study day start of treatment (MinASTDY)					
	N Rows	Mean	Std Dev	Min	Max	Median
PLACEBO	13	169.2	251	18	902	77
SA237	21	307.3	344.5	18	1132	198

Source: Join MinASTDT IV CS c ADSL MinASTDY By (TRT01P).jmp; CMROUTE_IV Subset of ACT2_SYSTEMIC CS Subset of EPOCH_RCP Subset of SCMINDC_RESCUE ubset of CMCAT_NMO_NMOSD Subset of ADCM 309 Ir.jmp

The mean and median duration of treatment with IV corticosteroid rescue therapy was approximately 3 days and a maximum of 5 to 7 days for both treatment groups ([Table 19](#)).

Table 19: Duration of IV corticosteroids rescue therapy, days, study 309

TRT01P	Treatment duration days					
	N Rows	Mean	Std Dev	Min	Max	Median
PLACEBO	13	3.154	1.068	2	5	3
SA237	21	3	1.761	0	7	3

Source: Join MinASTDY c full IV CS TRT Duration days By (TRT01P).jmp

Relapse disposition

There were 59 reported events in 48 subjects that represented potential relapses during the RCP. Thirteen events occurred in 9 subjects during the OLE. There were 20 events reported by investigators in subjects treated with placebo and 39 events in satralizumab-mwge subjects ([Table 20](#)). Most of these events had their blinded EDSS evaluation within 7 days. However, 18 of 20 events (90%) in the placebo group were determined to be protocol-defined relapses compared to 22 of 39 (56%) in the satralizumab-mwge group. Two of the events in the placebo group and 9 events in the satralizumab-mwge group were excluded due to alternate causes of the event. The remainder of those that were excluded in the satralizumab-mwge group did not meet the EDSS/FSS criteria for a protocol-defined event.

Table 20: Disposition of all clinical relapses, study 309

	TRT01P	
	PBO	SA237
Clinical relapses		
	20	39
EDSS within 7 days		
Missing	1 (5%)	4 (10%)
N	1 (5%)	3 (8%)

	TRT01P	
	PBO	SA237
Y	18 (90%)	32 (82%)
Protocol-defined relapse (PDR) (no 7-day limit)		
Missing	0	2 (5%)
N	2 (10%)	15 (39%)
Y	18 (90%)	22 (56%)
CEC-confirmed PDR		
missing	1 (5%)	4 (10%)
N	3 (15%)	14 (36%)
Y	16 (80%)	21 (54%)
Treated relapses		
N	0	12 (31%)
Y	20 (100%)	27 (69%)

Source: ADRLP 309

Of the 59 potential relapses, all but 5 had an EDSS assessment within 7 days, 2 in the placebo group, neither of which met the protocol criteria, and 3 in the satralizumab-mwge group, 2 of which did meet the criteria ([Table 21](#)).

Table 21: Disposition of clinical events by EDSS assessment interval, study 309

EDSSLE7*	RELAPSE	N Total		PLACEBO		SA237	
		N	%	N	%	N	%
N	N	3	5.1%	2	9.5%	1	2.6%
N	Y	2	3.4%	0	0.0%	2	5.3%
Y	N	19	32.2%	3	14.3%	16	42.1%
Y	Y	35	59.3%	16	76.2%	19	50.0%
Total		59	100.0%	21	100.0%	38	100.0%

Source: Join FDARPLPcADSL TRT01P By (EDSSLE7, RELAPSE)

*: EDSS done within 7 days

Of those events with a least a one-point increase on the EDSS, all but one qualified as a relapse. Of those without a one-point increase, a slightly higher proportion still qualified as a relapse ([Table 22](#)).

Table 22: Distribution of clinical events by 1-point increase on EDSS, study 309

PDRE1*	RELAPSE	Total		PLACEBO		SA237	
		N	%	N	%	N	%
N	N	21	35.6%	5	23.8%	16	42.1%
N	Y	16	27.1%	8	38.1%	8	21.1%
Y	N	1	1.7%	0	0.0%	1	2.6%

PDRE1*	RELAPSE	Total		PLACEBO		SA237	
		N	%	N	%	N	%
Y	Y	21	35.6%	8	38.1%	13	34.2%
Total		59	100.0%	21	100.0%	38	100.0%

Source: Join FDARPLPcADSL TRT01P By (PDRE1, RELAPSE)

*: One point or more increase in total EDSS

Reviewer Comment: Approximately 60% of the events in both groups did not have an EDSS increase of 1 or more; those events may have met other criteria for a protocol-defined relapse, such as an increase of 2 or more on one relevant FSS or an increase of one or more on two relevant FSS. A review of each of those criteria does not reveal any pattern of disproportionate confirmation of events that would favor either treatment group.

Of the initial or first relapses, there were 17 Clinical Relapses reported in the placebo group and 31 in the satralizumab-mwge group. Ninety-four percent (94%) were confirmed relapses with or without the 7-day limit for the EDSS assessment; 21 of the 31 (68%) of those in the satralizumab-mwge group were confirmed regardless of the 7-day limit and 19 of the 31 were confirmed with an EDSS assessment within the 7-day limit.

Table 23: Disposition of first relapses, study 309

First Relapse category	PBO	SA237
Clinical relapses	17	31
CEC-confirmed PDR (no 7-day limit)	16 (94%)	21 (68%)
CEC-confirmed PDR – EDSS within 7 days	16 (94%)	19 (61%)

Source: ADTTE by PARAM and CNSR

Reviewer Comment: As demonstrated in the analyses of the primary endpoint below, the statistical significance of the Time to First Event analysis is dependent on the disproportionate confirmation rate noted in the above tables.

Efficacy Results – Primary Endpoint

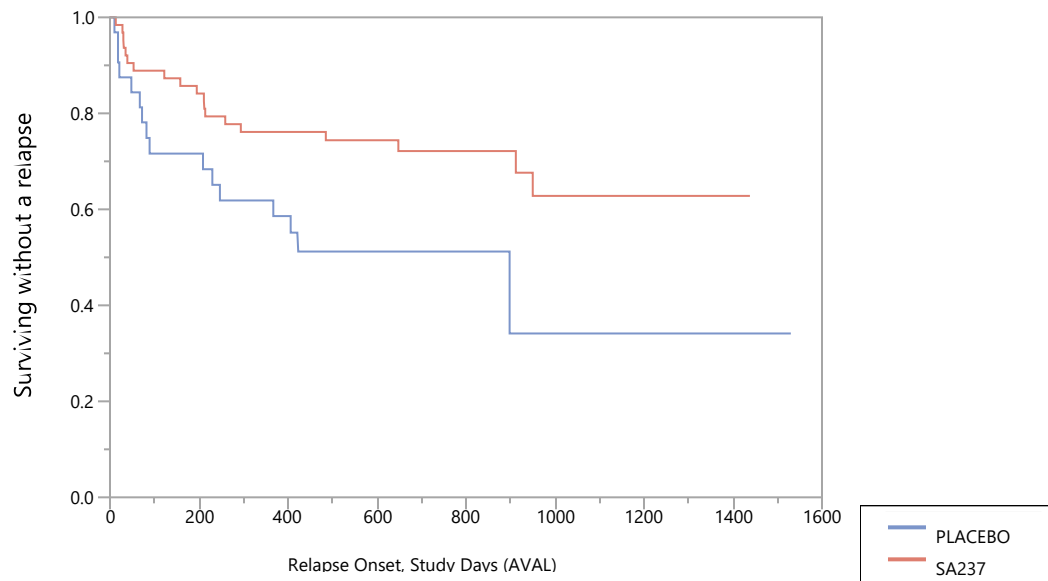
The primary endpoint was the time to the first protocol-defined relapse that was confirmed by the Clinical Events Committee and for which the EDSS/FSS assessment had been completed within 7 days of the subject report to the site. For the full ITT, treatment with satralizumab-mwge significantly delayed the onset ([Figure 1](#)). However, there was no benefit of satralizumab-mwge treatment for those who were seronegative ([Figure 2](#)). Of the 22 seronegative subjects treated with satralizumab-mwge, 10 had a CEC-confirmed relapse. Of 9 seronegative subjects treated with placebo, 3 had a relapse. The odds ratio and hazard ratio for

those who were seronegative favored the placebo group. The benefit is highly significant for those who were seropositive (**Figure 3**).

Figure 1: Time to first CEC-confirmed protocol-defined relapse, ITT, study 309

Product-Limit Survival Fit

Survival Plot



Time to event: AVAL
Censored by: CNSR
Censor Code: 1
Grouped by: TRT01P of ADTTE

Summary

Group	Number failed	Number censored	Odds ratio	HR (sponsor)
PLACEBO	16	16	0.432 P=0.0223	0.45 (0.23, 0.89) p=0.0184
SA237	19	44		
Combined	35	60		

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	5.2222	1	0.0223*
Wilcoxon	4.6595	1	0.0309*

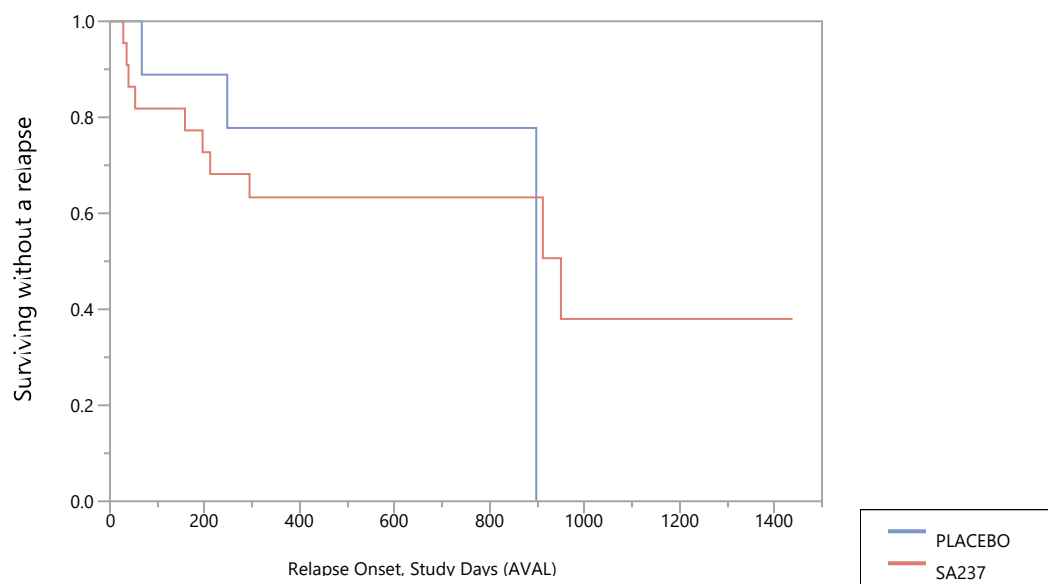
Source: TTE PDR01DB by TRT01P

Analysis of the primary endpoint by anti-AQP4 IgG serostatus

Figure 2: Time to first CEC-confirmed protocol-defined relapse, anti-AQP4 IgG seronegative, study 309

Product-Limit Survival Fit AQP4J=NEGATIVE

Survival Plot



Time to event: AVAL
Censored by: CNSR
Censor Code: 1
Grouped by: TRT01P of ADTTE

Summary

Group	Number failed	Number censored	Odds ratio	HR (sponsor)
PLACEBO	3	6	1.67	1.192
SA237	10	12		(0.298, 4.775)
Combined	13	18		p=0.8036

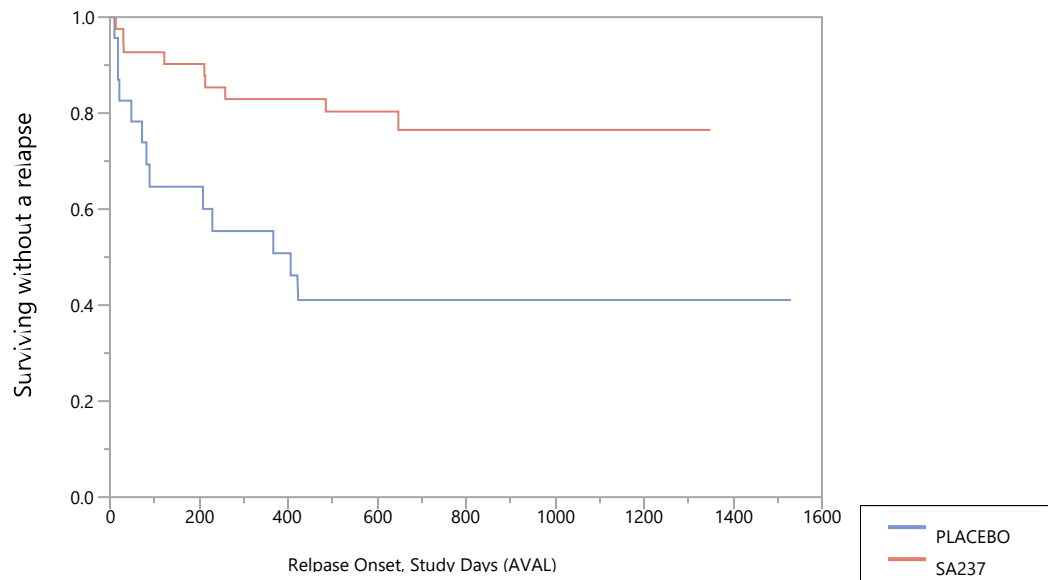
Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.0624	1	0.8028
Wilcoxon	0.5909	1	0.4421

Figure 3: Time to first CEC-confirmed relapse, anti-AQP4 IgG seropositive, study 309

Product-Limit Survival Fit AQP4J=POSITIVE

Survival Plot



Summary

Group	Number failed	Number censored	Odds ratio	HR (sponsor)
PLACEBO	13	10	0.216	0.261
SA237	9	32		(0.108, 0.627)
Combined	22	42		p=0.0014

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	9.9320	1	0.0016*
Wilcoxon	10.1534	1	0.0014*

Source: TTE PDR01DB by TRT01P group AQP4IgG status

Reviewer Comment: If all CEC-confirmed relapses are included, regardless of the 7-day limit to complete the EDSS assessment, the odds ratio for the AQP4+ subgroup would be 0.282, p=0.0039. If all Clinical Relapses, i.e. all relapses identified by the investigator, are included, the odds ratio for the AQP4+ subgroup would be 0.555, p=0.0855. If all Treated Relapses are included, the odds ratio for the AQP+ subgroup would be 0.299, p=0.0044.

Analyses of the primary endpoint by selected subgroups are shown in [Table 24](#). The result for each subgroup favors treatment with satralizumab-mwge.

Table 24: Primary endpoint by subgroups, study 309

Subgroup	ITT				Anti-AQP4 IgG seropositive adults			
	N	OR*, p-value**	HR, 95%CI	p-value	N	OR*, p-value**	HR***, 95%CI	p-value****
Full ITT	95	0.432 P=0.0023	0.450 (0.228, 0.889)	0.0184				
AQP4 IgG								
Negative	31	1.67 p = 8028	1.192 (0.298, 4.775)	0.8036				
Positive	64	0.216 p= 0.0016	0.261 (0.108, 0.627)	0.0014	64	0.216 p= 0.0016	0.261 (0.108, 0.627)	0.0014
SEX								
Female	77	0.516 p=0.0914			53	0.243 p=0.0062	0.271 (0.104, 0.706)	0.0045
Male	18	0.00 p=0.0436			11	0.00 p=0.0515	0.0 (0.00, NE)	0.0047
Age								
<50	64	0.607 p=0.2014			43	0.395 p=0.0856	0.403 (0.151, 1.076)	0.0619
≥50	31	0.197 p=0.0340			21	0.036 p=0.0032	0.093 (0.010, 0.854)	0.0103
Region								
US	48	0.231 p=0.0107		p=0.	34	0.618 p=0.3802	0.613 (0.167, 2.250)	0.4577
OUS	47	0.872	.	p=0.	30	0.059	0.097	0.0005

Subgroup	ITT				Anti-AQP4 IgG seropositive adults			
	N	OR*, p-value**	HR, 95%CI	p-value	N	OR*, p-value**	HR***, 95%CI	p-value****
		p=0.5658				p=0.007	(0.020, 0.470)	
US and Canada vs ROW								
US Canada	58	0.791 p=0.4350			40	0.467 P=0.1916		
ROW	37	0.130 p=0.0074			24	0.068 P=0.0031		
RACE								
White	59	0.268 P=0.0069			32	0.083 P=0.0012		
Non-white	36	0.9375 P=0.7945			32	0.563 P=0.3884		
RACE								
American Indian or Alaska native	2	SA237- 0:2†			2	SA237- 0:2†	NE	NE
Asian	14	0.286 P=0.0407			13	0.00 P=0.0109	0.00 (0.00, NE)	0.0042
Black or African American	16	SA 237 – 7:6† PBO – 0:3†			14	SA 237 – 5:6† PBO – 0:3†	73797218 (0.00, NE)	0.1448
Other	4				3		NE	NE
White	59	0.268 P=0.0069			32	0.0833 p=0.0012	0.169 (0.045, 0.629)	0.0027)
NMO Status								
NMO	71	0.480 P=0.0585	0.496 (0.234, 1.048)	0.0611	41	0.184 P=0.0021		
NMOSD	24	0.238 P=0.1727	0.369 (0.054, 2.539)	0.2985	23	0.256 P=0.1894		

Subgroup	ITT				Anti-AQP4 IgG seropositive adults			
	N	OR*, p-value**	HR, 95%CI	p-value	N	OR*, p-value**	HR***, 95%CI	p-value****
Previous therapy								
B-cell depleting therapy	12	0.6 P=0.7130	0.715 (0.119, 4.296)	0.7130	9	0.667 P=0.8188	0.795 (0.111, 5.675)	0.8188
Immunosuppressants and others	83	0.410 P=0.0183	0.415 (0.199, 0.868)	0.0159	55	0.176 P=0.0009	0.205 (0.078, 0.540)	0.0004
Most recent attack								
First attack	11	2.25 P=0.9970	0.995 (0.090, 11.018)	0.9970	9	0.750 P=0.7947	0.693 (0.043, 11.156)	0.7947
Relapse	84	0.347 0.0131	0.417 (0.205, 0.851)	0.0132	55	0.167 P=0.0006	0.236 (0.094, 0.594)	0.0010
Baseline EDSS								
≤5	74	0.314 P=0.0105			50	0.175 P=0.0030	0.228 (0.083, 0.630)	0.0020
>5	21	1.39 p=0.9043			14	0.429 0.3249	0.570 (0.065, 4.984)	0.6094

*: Reviewer unadjusted odds ratio

**: Log-Rank from Kaplan-Meier model

***: sponsor calculation

****: Cox proportional hazards model stratified for baseline ARR and geographic region

†: Failed:censored

1: Japanese and non-Japanese Asian

Data Quality and Integrity

There was a concern regarding access to the database after the “interim” database lock. The “interim” lock was for the primary analyses reported in the application. The database remained locked for all additional data collected, i.e. during the OLE. The sponsor provided a listing of all access to the database of both studies 309 and 307 up to and after the interim database lock. The sponsor reported that “The database on which the primary analysis for the BLA is based was not unlocked after the initial ‘interim’ lock”.

The sponsor was asked to detail the process of EDSS determination for the purpose of identifying relapses. Some changes were made to these EDSS scores in response to queries from the CRO that had responsibility for this process. It appears that none were made spontaneously by the site. Once the final data were sent to the CEC, there were subsequent changes made. However, the CEC reported by email that no changes to the adjudication decision were made due to these changes.

Efficacy Results – Secondary and other relevant endpoints

Change in Visual Analogue Scale for Pain from Baseline to Week 24

There was no improvement in the VAS measure of pain at 24 weeks ([Table 25](#)). The result was the same using imputation of baseline carried forward.

Table 25: VAS change at 24 weeks, study 309

TRT01P	N	Change in VAS (CHG)		
		Mean	Std Dev	Median
PLACEBO	20	-2.6	25.6	0
SA237	53	0.37	24	0

Source: AVISIT_WK24 Subset of PARAM_VASMM Subset of EPOCH_RCP Subset of ADVAS 309 CHG By (TRT01P).jmp

Change in FACIT fatigue scale score from baseline at week 24

There was a slight improvement in the FACIT total score at week 24 with satralizumab-mwge treatment but the difference was not statistically significant ([Table 26](#)).

Table 26: Change in FACIT total score at week 24, RCP, study 309

TRT01P	N Rows	Change in FACIT Total Score		
		Mean	Std Dev	Median
PLACEBO	20	1	10.3	0.5

TRT01P	N Rows	Change in FACIT Total Score		
		Mean	Std Dev	Median
SA237	54	2.94	8.48	2.5

Source: AVISIT_WK24 Subset of QSTEST_TOTAL Subset of QSCAT_FACIT Subset of EPOCH_RCP Subset of ADFACIT 309 CHG By (TRT01P).jmp

Relapse-free

At the end of the RCT, 78% of subjects treated with satralizumab-mwge were relapse-free, compared to 43.5% of placebo subjects ([Table 27](#)).

Table 27: Proportion relapse-free at end of RCT, anti-AQP4 positive adults, study 309

Relapse	N	Placebo		SA 237	
		N	%	N	%
Yes	22	13	56.5	9	22
No	42	10	43.5	32	78

Source: PDR01DB Subset of AQP4_seropos Subset of Join ADTTE 309 c ADSL 309 TRT01P By (CNSR).jmp

Reviewer Comment: The sponsor provided the above analysis in response to an AIR. The number of subjects who were relapse-free is the same as in the table above, with an HR of 0.26 (0.11, 0.63), $p=0.0014$.

Dose/Dose Response

Only one dose of satralizumab-mwge was studied.

Durability of Response

The durability of the response was not studied.

Persistence of Effect

The persistence of the response was not studied.

Additional Analyses Conducted on the Individual Trial

There were no additional efficacy analyses

6.2 Study 307JG; bn40898; A Multicenter, Randomized, Addition To Baseline Treatment, Double-Blind, Placebo-controlled, Phase 3 Study To Evaluate The Efficacy And Safety of Satralizumab-mwge (SA237) In Patients With Neuromyelitis Optica (NMO) And NMO Spectrum Disorder (NMOSD)

6.2.1 Study Design

Overview and Objective

The primary objective of this study was to demonstrate that the addition of satralizumab-mwge to ongoing immunotherapy was superior to the addition of placebo to ongoing immunotherapy as measured by the time to first protocol-defined protocol, confirmed by a Clinical Events Committee (CEC).

Trial Design

Patients were randomized 1:1 to either subcutaneous (SC) satralizumab-mwge at 120 mg or matching SC placebo at Weeks 0, 2 and 4, and Q4W thereafter, in combination with one of the following baseline treatments: azathioprine, mycophenolate mofetil or oral corticosteroids. Treatment with both oral corticosteroids and either azathioprine or mycophenolate mofetil was permitted for patients aged 12 to 17 years at the time of informed consent. The number of patients who were negative for anti-AQP4-IgG antibody at screening was intended to be limited to approximately 30% of the total adult (18 to 74 years at the time of informed consent) study population. Randomization was stratified by baseline ARR and geographical region. Patients without any relapse-prevention maintenance therapy could not be enrolled in the study.

Patients who experienced a relapse that was treated with rescue therapy and/or who experienced a protocol-defined relapse which was adjudicated by the CEC in the double-blind period or who completed the double-blind period had the option to enter the open-label extension (OLE) period. For those who had a treated or confirmed relapse, treatment in the OLE could start once neurologic status was stable for at least 31 but not longer than 60 days after the onset of relapse symptoms. For those who completed the double-blind period without a relapse, treatment in the OLE could begin at 4 weeks (± 7 days) after the last dose in the double-blind period. Those who withdrew from the double-blind phase after a relapse and chose not to enter the OLE were to continue safety follow-up (SFU) for 24 weeks (one year for those aged 12 to 17).

Reviewer Comment: For subjects who did not have a treated or confirmed relapse, the double-blind period continued until the protocol-defined end of the study, i.e. when 26 relapses had occurred.

Eligible patients were to be randomized at sites in Europe, Asia and North America. The double-blind phase was to continue until 26 relapses confirmed by the CEC had occurred. For subjects aged 12 to 17, enrollment was to continue until 8 patients had been enrolled.

An Independent Data Monitoring Committee (IDMC) performed periodic reviews of unblinded safety data and made a recommendation as to whether the trial should continue.

Eligibility

1. The criteria for a diagnosis of NMO or NMOSD were the same as in study 309
2. Clinical evidence of at least 2 documented relapses (including first attack) in the last 2 years prior to screening, at least one of which has occurred in the 12 months prior to screening.
3. Expanded Disability Status Scale (EDSS) score from 0 to 6.5 inclusive at screening.
4. Age 12 to 74 years, inclusive at the time of informed consent.
5. One of the following baseline treatments must be at stable dose as a monotherapy for 8 weeks prior to baseline
 - a. Azathioprine
 - b. Mycophenolate mofetil
 - c. Oral corticosteroids

For subjects aged 12 to 17 years, either azathioprine or mycophenolate plus corticosteroids were allowed.

Reviewer Comment: Exclusion criteria were essentially that same as those for study 309.

Relapse Assessment

At the time of a patient report of signs and symptoms consistent with a potential relapse, the treating investigator was to request that an EDSS assessment be performed by an independent examining assessor. The independent EDSS assessor was to have no access to the patient's clinical data. The treating investigator indicated in the relapse assessment form (RAF) and the eCRF whether the relapse met the criteria of a Protocol Define Relapse (PDR). However, all cases of a potential relapse reported by the treating investigator ("clinical relapses") during the double-blind period (irrespective of whether indicated as PDR or not) were independently assessed by the CEC to determine if the PDR criteria were met, based on a dossier consisting of the RAF and the EDSS/FSS scoring forms of the actual relapse assessment and the preceding visit.

The criteria for a new or worsened neurologic deficit were:

- An increase of at least 1.0 point on the EDSS score excepting increase to 1.0 or 1.5 from zero (i.e., a 2.0-point increase on the EDSS is required if the baseline was zero)
- An increase of at least 2.0 points on one of the appropriate 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

Reviewer Comment: The criteria were the same as those for study 309.

Treatment

Results from a Phase 1 single dose study in healthy subjects and a multiple dose study in patients with Rheumatoid Arthritis showed that satralizumab-mwge at a dose of 120 mg SC Q4W inhibited IL-6 signaling completely, whereas lower doses (30, 60 mg SC Q4W) did not. The same dose was used for adults and adolescents.

The dose of azathioprine was 3 mg/kg/day

The dose of mycophenolate was 3000 mg/day

Oral corticosteroids were given at 15 mg/day of prednisolone or the equivalent

Study Endpoints

Primary Endpoint

The primary endpoint was the time to first relapse that had been evaluated by the independent EDSS assessor within 7 days after relapse symptoms had been reported to the site by the subject. The onset of the relapse was defined as the day of onset of symptoms as reported by the subject. Time to the event is based on the date of randomization and the date of onset of new symptoms. Subjects were censored at the end of the double-blind period, or at the time of the start of a new therapy or increased dose of existing therapy for NMOSD, or the start of rescue therapy.

The analysis of safety includes an analysis of the "All-Subjects-Treated" (All SA237) population, defined as all enrolled subjects who were treated with at least one dose of active study drug at any time. The date of the first active study drug administration in the double-blind phase, or the first dose in the OLE for those randomized to placebo during the double-blind phase, are defined as Day 1 for the All SA237 analysis.

Secondary Endpoints

Analysis of change in VAS for pain score from baseline at week 24 using ANCOVA.
Analysis of change in FACIT fatigue scale score from baseline at week 24 using ANCOVA.

Statistical Analysis Plan

Sample size

The estimated sample size was 70 based on the estimated recruitment rate and time to reach 26 relapses. Accrual of 26 relapses was based on the following assumptions:

- A two-sided log-rank test
- 80% power at the 5% significance level
- A 66.5% reduction in the risk of relapse, i.e. the TFR hazard ratio of SA237 over placebo of 0.335
- TFR in the placebo arm following an exponential distribution, with hazard rate for one-year $h(t) = 0.4184$
- A 2-year dropout rate of 10%

The primary endpoint was analyzed for the Intent to Treat (ITT) population, defined as all randomized subjects. Subjects without a relapse were censored at the end of the double-blind period or at the time that concurrent immunotherapy was changed. Treated relapses were censored at the start of rescue therapy. The analysis is adjusted for baseline ARR (one vs. more than one) and geographical area (Asia vs. EU/other).

Protocol Amendments

Version 2

- Adolescent patients were required to be positive for anti-AQP4-IgG antibody
- Changed the eligible age range to 12 to 74 years old from 18 to 74 years old
- Changed the exclusion for White Blood Cell Count to $<3.0 \times 10^3/\mu\text{L}$ from $<4.0 \times 10^3/\mu\text{L}$

Version 3

- C-SSRS added

Version 4

- Limited the proportion of anti-AQP4 IgG antibody seropositive subjects to $<30\%$

Version 5

Clinical Review
Lawrence Rodichok MD
BLA 761149
Enspryng/satralizumab-mwge

- Extended the duration of treatment in OLE from one year to the time of commercial availability

Version 6

- All screening assessments must be completed within 28 days of baseline

Version 7

- Reduced the target number of adolescents to 6 from 8

Version 8

- Changes related to the Pre-filled pen

6.2.2 Study Results

Compliance with Good Clinical Practices

The sponsor reports that this study was conducted in accordance with the Declaration of Helsinki and the International Council on Harmonization principles of Good Clinical Practice.

Financial Disclosure

One investigator at one site (b) (6) reported payments of other sorts. The site randomized (b) (6) subjects, (b) (6) to placebo and (b) (6) to SA237. No subject had a relapse. There were no investigators with any other type of financial arrangement.

Subject Disposition

83 patients were enrolled; 83 were randomized 1:1, and 83 received at least one dose of study drug. The first patient was enrolled on February 20, 2014. The Last patient Last Visit and the Clinical Cut-off Date (CCOD) were June 6, 2018 which was the date of the 26th protocol-defined relapse. Database lock was August 10, 2018. The planned and actual treatment was the same for all subjects.

Patients were enrolled at 34 sites in 11 countries.

Two sites enrolled 9 patients, one enrolled 8, and 2 sites enrolled 5 patients. Most sites enrolled one or two patients (Table 28). Randomization was generally balanced between treatment groups by site, with the exception of site 5106, at which 7 patients were randomized to placebo and 2 to satralizumab-mwge.

Table 28: Number of patients randomized by number of sites

Number randomized (N Rows)	Number of sites (SITEID)
1	17
2	8
3	2
4	2
5	2
8	1
9	2

Source: ADSL 307 By (SITEID) By (N Rows).jmp

The 10 sites with the highest number of CEC-confirmed relapses accounted for 77.8% of the confirmed relapses in the satralizumab-mwge treatment group compared to 52.6% of the confirmed relapses in the placebo group ([Table 29](#)).

Reviewer Comment: No single site or group of sites appear to have disproportionately influenced the primary outcome result.

Table 29: Number of CEC-confirmed relapses, by treatment group, top 10 sites

SITEID	Placebo		SA237	
	N	%	N	%
3405*	1	5.3%	3	33.3%
5106*	0	0.0%	0	0.0%
3410*	2	10.5%	1	11.1%
5205*	2	10.5%	1	11.1%
5203	1	5.3%	0	0.0%
3408	1	5.3%	1	11.1%
3303*	1	5.3%	0	0.0%
1102	1	5.3%	0	0.0%
3801	0	0.0%	1	11.1%
5101	1	5.3%	0	0.0%
Top 10	10	52.6%	7	77.8%
All Confirmed Relapses	19	100.0%	9	100.0%

Source: ADRLP 307 PDRCEFLbyTRT01P By (SITEID)

*: highest 5 enrolling sites

The highest 2 enrolling countries, Poland and Japan, accounted for over 50% of the randomized patients ([Table 30](#)).

Table 30: Randomization by country and treatment group, ITT

Country	PLACEBO	SA237	Subjects(filtered)
POL	9 (21.4%)	14 (34.1%)	23 (27.7%)
JPN	11 (26.2%)	11 (26.8%)	22 (26.5%)
TWN	7 (16.7%)	5 (12.2%)	12 (14.5%)
ITA	6 (14.3%)	3 (7.3%)	9 (10.8%)
DEU	2 (4.8%)	2 (4.9%)	4 (4.8%)
AUS	3 (7.1%)	0 (0.0%)	3 (3.6%)
UKR	0 (0.0%)	3 (7.3%)	3 (3.6%)
USA	2 (4.8%)	0 (0.0%)	2 (2.4%)
GBR	1 (2.4%)	1 (2.4%)	2 (2.4%)
HUN	1 (2.4%)	1 (2.4%)	2 (2.4%)
FRA	0 (0.0%)	1 (2.4%)	1 (1.2%)
Subjects(filtered)	42 (100.0%)	41 (100.0%)	83 (100.0%)
1stColItemSubjects	42 (100.0%)	41 (100.0%)	(Denom=1stColTot)

Source: JRev307SelADSLITTFL_Y COUNTRYbyTRT01P

The disposition of subjects during the double-blind portion of the trial is summarized in [Table 31](#).

Of the 42 randomized to placebo, 30 subjects completed the randomized controlled phase (RCP), 10 discontinued and 2 were ongoing in the RCP period at the time of CCOD. The reasons for discontinuation are listed in the table.

Of the 41 randomized to satralizumab-mwge, 31 completed subjects completed the RCP, 3 discontinued, and 7 were ongoing in the RCP at the time of CCOD. All three discontinuations were due to an AE.

Table 31: Disposition of subjects, double-blind period, ITT

End of Treatment Status in Period 01	PLACEBO	SA237
Completed	30 (71.4%)	31 (75.6%)
Discontinued	10 (23.8%)	3 (7.3%)
Adverse Event	5 (11.9%)	3 (7.3%)
Eligibility Violation	1 (2.4%)	0 (0.0%)
Non-Compliance with Study Drug	2 (4.8%)	0 (0.0%)
Withdrawal by Subject	2 (4.8%)	0 (0.0%)
Ongoing	2 (4.8%)	7 (17.1%)
Subjects(filtered)	42 (100.0%)	41 (100.0%)
1stColItemSubjects	42 (100.0%)	41 (100.0%)

Source: JRev307 EOT01STTbyTRT01P; JRev307 DCP01RSbyTRT01P

The disposition for the subgroup of adult subjects who were anti-AQP4 IgG seropositive is shown in [Table 32](#). In this subgroup, 26 were randomized to satralizumab-mwge and 26 to placebo. Of the 26 placebo subjects, 17 (65.4%) completed the RCP, 8 (30.8%) discontinued and one was considered ongoing at the time of CCOD. Of the 26 randomized to satralizumab-mwge, 17 (65.4%) completed the RCP, 3 (11.5%) discontinued, and 6 (23.1%) were considered ongoing at the time of CCOD.

Table 32: Disposition of subjects, anti-AQP4 IgG seropositive adults, study 307

EOT Status in Period 01	PLACEBO	SA237
Completed	17 (65.4%)	17 (65.4%)
Discontinued	8 (30.8%)	3 (11.5%)
Adverse Event	4 (15.4%)	3 (11.5%)
Eligibility Violation	1 (3.8%)	0 (0.0%)
Non-Compliance with Study Drug	2 (7.7%)	0 (0.0%)
Withdrawal by Subject	1 (3.8%)	0 (0.0%)
Ongoing	1 (3.8%)	6 (23.1%)
Subjects(filtered)	26 (100.0%)	26 (100.0%)
1stColltemSubjects	26 (100.0%)	26 (100.0%)

Source: JRev307SelAGEGR1_18 AQP4J_SEROPOS EOT01STTbyTRT01P; JRev307SelAGEGR1_18 AQP4J_SEROPOS DCP01RSbyTRT01P

Protocol Violations/Deviations

There were relatively few major protocol deviations ([Table 33](#)). The majority were related to study-related visits or procedures that occurred outside of the allowed time window. The informed consent issues were not major. Two involved the version of the ICF or consent for a sub-study. One involved the assent from a subject under age 18. The only significant issue involving eligibility was for subject (b) (6) who did not meet inclusion criterion 1 because the MRI report indicated “that Dawson fingers and Juxtacortical lesions are detected” suggesting that the subject might have had MS. This subject was randomized to SA237 but was anti-AQP4 IgG seronegative and, therefore, will not impact the analysis of the population for which satralizumab-mwge would be indicated if approved.

Table 33: Major protocol deviations, study 307

Protocol Deviation Coded Term	PLACEBO	SA237
AE SAE	1 (2.4%)	0 (0.0%)
DISALLOWED MEDICATIONS	0 (0.0%)	2 (4.9%)
INC/EXCL CRITERIA	1 (2.4%)	5 (12.2%)
INFORMED CONSENT	0 (0.0%)	3 (7.3%)
IP ADMIN/STUDY TREAT	5 (11.9%)	4 (9.8%)
IP ADMIN/STUDY TREATMENT	0 (0.0%)	1 (2.4%)
PROCEDURES/TESTS	20 (47.6%)	24 (58.5%)
VISIT SCHEDULE	2 (4.8%)	0 (0.0%)

Protocol Deviation Coded Term	PLACEBO	SA237
Subjects(filtered)	24 (57.1%)	28 (68.3%)
1stCollItemSubjects	42 (100.0%)	41 (100.0%)

Source: JRev307SelITTF_L_Y DVDECODbyTRT01PfiltDVCAT_MAJOR

Reviewer Comment: *The number and type of protocol deviations are unlikely to affect interpretation of the key efficacy and safety analyses.*

Table of Demographic Characteristics

The basic demographic characteristics for the full ITT are listed in [Table 34](#). In general, the treatment arms were well balanced for the essential demographic characteristics. The population was nearly all female. The mean age was 43.4 years in the placebo group vs. 40.8 in the satralizumab-mwge group. More subjects in the placebo group were over 40 years old (69%) compared to 51.2% of the satralizumab-mwge group. Approximately half of the subjects were of the white race and essentially all were non-Hispanic. Subjects were evenly distributed between Asia and Europe with few from the United States (US).

Table 34: Demographics, ITT population, study 307

Subgroup	PLACEBO (N = 42) n (%)	SA237 (N = 41) n (%)	Total (N = 83) n (%)
Sex			
Female	40 (95.2)	37 (90.2)	77 (92.8)
Male	2 (4.8)	4 (9.8)	6 (7.2)
Age			
Mean	43.38	40.78	42.1
Standard Deviation	12.03	16.09	14.16
Minimum	14	13	13
Median	44	41	42
Maximum	65	73	73
Age Group			
Under 40 (AGE < 40)	13 (31.0)	20 (48.8)	33 (39.8)
Over 40 (40 <= AGE)	29 (69.0)	21 (51.2)	50 (60.2)
Race			
Asian	18 (42.9)	17 (41.5)	35 (42.2)
Black or African American	2 (4.8)	0 (0.0)	2 (2.4)
Other	1 (2.4)	0 (0.0)	1 (1.2)
White	21 (50.0)	24 (58.5)	45 (54.2)

Subgroup	PLACEBO (N = 42) n (%)	SA237 (N = 41) n (%)	Total (N = 83) n (%)
Ethnicity			
Missing	2 (4.8)	0 (0.0)	2 (2.4)
Not Hispanic or Latino	40 (95.2)	41 (100.0)	81 (97.6)
Region			
Asia	18 (42.9)	16 (39.0)	34 (41.0)
Europe	19 (45.2)	25 (61.0)	44 (53.0)
Other	3 (7.1)	0 (0.0)	3 (3.6)
United States	2 (4.8)	0 (0.0)	2 (2.4)

Source: OCS DM_TOOL 307

The demographic characteristics of the adult population who were anti-AQP4 IgG seropositive are listed in [Table 35](#). The mean age and proportion over 40 years old is slightly higher compared to the full ITT.

Table 35: Demographic characteristics, anti- AQP4 IgG seropositive adults, study 307

Subgroup	PLACEBO (N = 26) n (%)	SA237 (N = 26) n (%)	Total (N = 52) n (%)
Sex			
Female	26 (100.0)	26 (100.0)	52 (100.0)
Age			
Mean	45.62	45.62	45.62
Standard Deviation	10.45	14.71	12.63
Minimum	23	21	21
Median	47	44.5	45.5
Maximum	65	73	73
Age Group			
Age Group 1 (AGE < 40)	8 (30.8)	9 (34.6)	17 (32.7)
Age Group 2 (40 <= AGE)	18 (69.2)	17 (65.4)	35 (67.3)
Race			
Asian	13 (50.0)	14 (53.8)	27 (51.9)
Other	1 (3.8)	0 (0.0)	1 (1.9)
White	12 (46.2)	12 (46.2)	24 (46.2)
Ethnicity			
Not Hispanic or Latino	26 (100.0)	26 (100.0)	52 (100.0)
Region			

Subgroup	PLACEBO (N = 26) n (%)	SA237 (N = 26) n (%)	Total (N = 52) n (%)
Asia	13 (50.0)	13 (50.0)	26 (50.0)
Europe	13 (50.0)	13 (50.0)	26 (50.0)

Source: DMTOOL 307 AQP4pos and 18or over

Medical History

The previous medical conditions that were concurrent during the trial are listed in [Table 36](#). Because of the known increased incidence of autoimmune disorders in patients with NMOSD, the proportion of subjects with a concurrent musculoskeletal or connective tissue disorder is listed in [Table 37](#). The treatment arms are balanced for most common disorders and those that are disproportionate to one treatment group are not likely to affect interpretation of efficacy or safety.

Table 36: Concurrent medical conditions, ITT, 5% or more of either group, study 307

Dictionary Derived Term	PLACEBO	SA237
Hyperlipidaemia	1 (2.4%)	7 (17.1%)
Constipation	7 (16.7%)	7 (17.1%)
Insomnia	6 (14.3%)	6 (14.6%)
Depression	2 (4.8%)	5 (12.2%)
Osteoporosis	4 (9.5%)	5 (12.2%)
Iron deficiency anaemia	4 (9.5%)	4 (9.8%)
Gastritis	3 (7.1%)	4 (9.8%)
Hypertension	6 (14.3%)	4 (9.8%)
Seasonal allergy	5 (11.9%)	4 (9.8%)
Back pain	0 (0.0%)	4 (9.8%)
Spinal osteoarthritis	0 (0.0%)	3 (7.3%)
Muscular weakness	0 (0.0%)	3 (7.3%)
Diabetes mellitus	2 (4.8%)	3 (7.3%)
Cataract	2 (4.8%)	3 (7.3%)
Hypoaesthesia	0 (0.0%)	3 (7.3%)
Hypercholesterolaemia	4 (9.5%)	3 (7.3%)
Gastroesophageal reflux disease	3 (7.1%)	3 (7.3%)
Dysuria	0 (0.0%)	3 (7.3%)
Headache	6 (14.3%)	2 (4.9%)
Autoimmune thyroiditis	4 (9.5%)	0 (0.0%)
Anaemia	4 (9.5%)	0 (0.0%)
Drug hypersensitivity	3 (7.1%)	1 (2.4%)
Intervertebral disc protrusion	3 (7.1%)	1 (2.4%)
Sjogren's syndrome	3 (7.1%)	1 (2.4%)
Subjects(filtered)	36 (85.7%)	31 (75.6%)
1stColItemSubjects	42 (100.0%)	41 (100.0%)

Source: JRev307 MHDECODbyTRT01PfiltMHCAT_MEDHX ATIREL_CONCOM

Table 37: Concurrent musculoskeletal and connective tissue disorders, ITT, study 307

Dictionary Derived Term	PLACEBO	SA237	Subjects(filtered)
Osteoporosis	4 (9.5%)	5 (12.2%)	9 (10.8%)
Back pain	0 (0.0%)	4 (9.8%)	4 (4.8%)
Spinal osteoarthritis	0 (0.0%)	3 (7.3%)	3 (3.6%)
Muscular weakness	0 (0.0%)	3 (7.3%)	3 (3.6%)
Osteoarthritis	1 (2.4%)	2 (4.9%)	3 (3.6%)
Intervertebral disc disorder	1 (2.4%)	2 (4.9%)	3 (3.6%)
Arthralgia	2 (4.8%)	2 (4.9%)	4 (4.8%)
Pain in extremity	0 (0.0%)	2 (4.9%)	2 (2.4%)
Intervertebral disc protrusion	3 (7.1%)	1 (2.4%)	4 (4.8%)
Joint stiffness	0 (0.0%)	1 (2.4%)	1 (1.2%)
Muscle spasms	0 (0.0%)	1 (2.4%)	1 (1.2%)
Spondylitis	0 (0.0%)	1 (2.4%)	1 (1.2%)
Myositis	0 (0.0%)	1 (2.4%)	1 (1.2%)
Osteonecrosis	0 (0.0%)	1 (2.4%)	1 (1.2%)
Scleroderma	0 (0.0%)	1 (2.4%)	1 (1.2%)
Sjogren's syndrome	3 (7.1%)	1 (2.4%)	4 (4.8%)
Temporomandibular joint syndrome	0 (0.0%)	1 (2.4%)	1 (1.2%)
Connective tissue disorder	1 (2.4%)	0 (0.0%)	1 (1.2%)
Musculoskeletal stiffness	1 (2.4%)	0 (0.0%)	1 (1.2%)
Systemic lupus erythematosus	1 (2.4%)	0 (0.0%)	1 (1.2%)
Subjects(filtered)	15 (35.7%)	14 (34.1%)	83 (100.0%)
1stColItemSubjects	42 (100.0%)	41 (100.0%)	(Denom=1stColTot)

Source: JRev307 MHDECODbyTRT01PfiltMHCAT_MEDHX ATIREL_CONCOM MHSOC_MUSCSKEL

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline Disease Characteristics

Approximately two-thirds of subjects were seropositive for the anti-AQP4 IgG antibody at baseline. The median EDSS at baseline was 3.5 for both treatment groups. Sixty-nine percent of the placebo group and 78% of the satralizumab-mwge group had some type of therapy for NMOSD in the past. These characteristics were adequately balanced by treatment group ([Table 38](#)). The baseline disease characteristics for adults who were anti-AQP4 antibody seropositive are listed in [Table 39](#). These characteristics were similar to those of the full ITT. A somewhat lower proportion of these subjects had been treated previously.

Table 38: Baseline NMOSD characteristics, ITT, study 307

Characteristic	Placebo		SA237	
	n	%	N	%
AQP4-IgG status at baseline				

Characteristic	Placebo		SA237	
	n	%	N	%
Positive	28	66.7	27	65.9
NMO diagnosis				
NMO	28	66.7	33	80.5
NMOSD	14	33.3	8	19.5
Baseline ARR category				
One	20	47.6	20	48.8
More than one	22	52.4	21	51.2
Previous therapy (CMCLAS)*				
Glucocorticoids	25	59.5	26	63.4
Other Immunosuppressants	15	35.7	11	26.8
Selective Immunosuppressants	5	11.9	3	7.3
Others	12	28.6	11	26.8
Any previous therapy	29	69.0	32	78.0
Baseline ARR				
Mean ±SD	1.57±0.62		1.57±0.54	
Median	1.5		1.5	
Min, Max	1, 4		1, 3	
Baseline EDSS				
Mean ±SD	3.63±1.32		3.83±1.57	
Median	3.5		3.5	
Min, Max	1.5, 6.5		1, 6.5	

*: previous and not concurrent

Anti-AQP4 IgG seropositive adults

Table 39: Baseline NMOSD characteristics, anti-AQP4 IgG adults, study 307

Characteristic	Placebo		SA237	
	n	%	N	%
NMO diagnosis				
NMO	14	53.8	18	69.2
NMOSD	12	46.2	8	30.8
Baseline ARR category				
One	15	57.7	14	53.8
More than one	11	42.3	12	46.2
Previous therapy				
Glucocorticoids	16	38.1	17	41.5
Other Immunosuppressants	8	19.0	8	19.5
Selective Immunosuppressants	2	4.8	2	4.9
Others	6	14.3	10	24.4
Any previous therapy	17	40.5	21	51.2
Baseline ARR				
Mean ±SD	1.35±0.42		1.62±0.55	
Median	1.25		1.5	
Min, Max	1, 2.5		1, 3	
Baseline EDSS				
Mean ±SD	3.72±1.49		4.21±1.54	
Median	3.5		4	

Characteristic	Placebo		SA237	
	n	%	N	%
Min, Max	1.5, 6.5		1, 6.5	

*: previous and not concurrent

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Compliance was calculated according to the SAP as the number of SC injections during the RCP divided by the number of planned SC injections during the RCP times 100%. The compliance rate for satralizumab-mwge and placebo was essentially 100% (Table 40). One satralizumab-mwge subject had a compliance rate under 90%.

Table 40: Compliance rate, ITT, study 307

TRT01P	N	Compliance*					
		Mean	Std Dev	Min	Max	Median	N Missing
PLACEBO	42	99.8	1.64	95.2	104	100	0
SA237	41	98.8	3.52	78.9	102	100	0

Source: Join ADSL307 c RCP EPOCH SUMDOSE by USUBJID of ADEX Compliance By (TRT01P).jmp

*: number of doses/number of expected doses ((Treatment duration/28) +2 if duration ≥15; else = 1) X 100

Concurrent medications during the RCP

Baseline relapse prevention

ITT

As required by protocol, subjects were being treated with either azathioprine, or mycophenolate, or corticosteroids for relapse prevention along with either satralizumab-mwge or placebo during the RCP. Subjects in the 12 to 17-year old age group were treated with either azathioprine or mycophenolate plus corticosteroids. Corticosteroids alone was the most common concurrent therapy, followed by azathioprine and mycophenolate (Table 41). For the population of adults who were anti-AQP4 IgG seropositive, corticosteroids alone or azathioprine alone were the most common ongoing therapies during the RCP (Table 42).

Table 41: Concurrent relapse prevention, ITT, study 307

CMTRT (ADSL TRTBL)	PLACEBO	SA237
AZATHIOPRINE	13 (31.0%)	16 (39.0%)
AZATHIOPRINE + ORAL CORTICOSTEROIDS	0 (0.0%)	3 (7.3%)
MYCOPHENOLATE MOFETIL	8 (19.0%)	4 (9.8%)
MYCOPHENOLATE MOFETIL + ORAL CORTICOSTEROIDS	1 (2.4%)	1 (2.4%)
ORAL CORTICOSTEROIDS	20 (47.6%)	17 (41.5%)

CMTRT (ADSL TRTBL)	PLACEBO	SA237
Subjects(filtered)	42 (100.0%)	41 (100.0%)
1stCollItemSubjects	42 (100.0%)	41 (100.0%)

Source: JRev307 CMTRTbyTRT01PfiltCMCAT_BLMATRNX

Table 42: Concurrent relapse prevention, anti-AQP4 IgG seropositive adults, study 307

TRTBL	PLACEBO	SA237
AZATHIOPRINE	11 (42.3%)	11 (42.3%)
MYCOPHENOLATE MOFETIL	2 (7.7%)	1 (3.8%)
ORAL CORTICOSTEROIDS	13 (50.0%)	14 (53.8%)
Subjects(filtered)	26 (100.0%)	26 (100.0%)
1stCollItemSubjects	26 (100.0%)	26 (100.0%)

Source: JRev307SelAGEGR1_18 AQP4J_SEROPOS TRTBLbyTRT01P

Other concomitant medications not for NMOSD

The most common medications taken concurrently during the RCP that were not for treatment of NMOSD are listed by ATC1 category in [Table 43](#). Drugs for gastrointestinal acid related disorders, systemic antibiotics and anti-inflammatory drugs were most common and generally balanced by treatment group. However, there appeared to be greater use of drugs in the respiratory and cardiovascular categories for those treated with satralizumab-mwge. The use of anti-histamines and other drugs for upper airway symptoms for treatment of an adverse event was more common in those treated with satralizumab-mwge ([Table 44](#)).

Table 43: Concurrent medications by ATC1 category, not for NMOSD, ITT, study 307

ATC1	PLACEBO	SA237
ALIMENTARY TRACT AND METABOLISM	27 (64.3%)	26 (63.4%)
ANTIINFECTIVES FOR SYSTEMIC USE	25 (59.5%)	24 (58.5%)
NERVOUS SYSTEM	20 (47.6%)	21 (51.2%)
MUSCULO-SKELETAL SYSTEM	20 (47.6%)	20 (48.8%)
RESPIRATORY SYSTEM	10 (23.8%)	17 (41.5%)
CARDIOVASCULAR SYSTEM	8 (19.0%)	15 (36.6%)
BLOOD AND BLOOD FORMING ORGANS	11 (26.2%)	14 (34.1%)
DERMATOLOGICALS	10 (23.8%)	7 (17.1%)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	4 (9.5%)	7 (17.1%)
VARIOUS	10 (23.8%)	6 (14.6%)
SENSORY ORGANS	1 (2.4%)	5 (12.2%)
GENITO URINARY SYSTEM AND SEX HORMONES	5 (11.9%)	3 (7.3%)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	0 (0.0%)	1 (2.4%)
ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS	1 (2.4%)	0 (0.0%)
Subjects(filtered)	39 (92.9%)	36 (87.8%)
1stCollItemSubjects	42 (100.0%)	41 (100.0%)

Source: JRev307 ATC1byTRT01PfiltATIREL_CONCOM EPOCH_RCP CMCAT_OTHERRX

Table 44: Concomitant drugs for the treatment of an adverse event, respiratory category, ITT, study 307

ATC2	PLACEBO		SA237	
	N	%	N*	%
Antihistamines for Systemic Use	2	4.8%	10	24.4%
Cough and Cold Preparations	4	9.5%	5	12.2%
Drugs for Obstructive Airway Diseases	1	2.4%	2	4.9%
Nasal Preparations	2	4.8%	5	12.2%
Throat Preparations	0	0.0%	2	4.9%
All use	9	21.4%	24	58.5%

Source: CMINDC_AE ATC1_RESP ATIREL_CONCOM EPOCH_RCP CMCAT_OTHER ADCM 307 By (USUBJID, ATC2, TRT01P)
NUSUBJIDbyTRT01P By ATC2

*: N = NUSUBJID

Reviewer Comment: It appears that anti-histamines were used more frequently in the satralizumab-mwge group to treat an adverse event compared to the placebo group. The more frequent use of drugs in the ATC1 category “cardiovascular” does not correlate with any single group of drugs in ATC2.

Rescue medication

The use of glucocorticoids for rescue treatment of a relapse is listed by treatment group in [Table 45](#). As expected from the proportion of subjects with a relapse, use was more frequent in the placebo group.

Table 45: The use of rescue medication for relapse treatment, ITT, study 307

CMCLAS	PLACEBO	SA237
GLUCOCORTICOIDS	23 (54.8%)	17 (41.5%)
OTHER BLOOD PRODUCTS	5 (11.9%)	3 (7.3%)
SOLUTIONS PRODUCING OSMOTIC DIURESIS	1 (2.4%)	0 (0.0%)
MONOCLONAL ANTIBODIES	1 (2.4%)	0 (0.0%)
Subjects(filtered)	25 (59.5%)	18 (43.9%)
1stCollItemSubjects	42 (100.0%)	41 (100.0%)

Source: JRev307 CMCLASbyTRT01PfiltATIREL_CONCOM EPOCH_RCP CMINDC_RESCUE

Disposition of Relapses

During the RCP there were 47 potential relapses recorded in the CRF in 45 subjects, 27 events in 27 subjects in the placebo group and 20 events in 18 subjects in the satralizumab-mwge group. Thirteen events occurred in 9 subjects during the OLE.

After further clinical assessment by the investigator for confounding clinical factors such as an intercurrent illness, and after determination of the EDSS score by the independent assessor, 20 of the 27 events (74.1%) in the placebo group and 13 of the 20 events (65%) in the satralizumab-mwge group were considered a protocol-defined relapse by the investigator. Three of the events in the placebo group and one in the satralizumab-mwge group were attributed to concurrent clinical factors. The remaining events determined to not represent protocol-defined relapses were excluded because they did not meet the clinical criteria for a new or worsening neurologic deficit. (Table 46).

A higher proportion these events that occurred in the placebo group (93%) had their blinded EDSS evaluation within 7 days compared to the satralizumab-mwge group (75%). 20 of 27 events (74%) in the placebo group were determined to be protocol-defined relapses compared to 13 of 20 (65%) in the satralizumab-mwge group. Three of the events in the placebo group and 1 event in the satralizumab-mwge group were excluded due to alternate causes of the event. The remainder of those that were excluded did not meet the EDSS/FSS criteria for a protocol-defined event.

Table 46: Disposition of clinical relapses, RCP, study 307

	TRT01P	
	PBO	SA237
Clinical relapses		
	27	20
EDSS within 7 days		
N	2 (7%)	5 (25%)
Y	25 (93%)	15 (75%)
Protocol-defined relapse (PDR) (no 7-day limit)		
N	7 (26%)	7 (35%)
Y	20 (74%)	13 (65%)
CEC-confirmed PDR		
N	8 (30%)	11 (55%)
Y	19 (70%)	9 (45%)
Treated relapses		
N	0	12 (31%)
Y	20 (100%)	27 (69%)

Source: ADRLP 307

First Relapses

For the full ITT, the CEC confirmed 19 of the 27 (70.4%) first clinical relapses in the placebo group and 9 of the 18 (50%) first clinical relapses in the satralizumab-mwge group. Restriction to those relapses that were confirmed by the CEC and for which the EDSS/FSS assessment occurred within 7 days of the subject relapse report reduces the number of relapses to be included in the primary analysis by one in each treatment group ([Table 47](#)). The disposition of relapses for the anti-AQP4 IgG seropositive adult population is shown in [Table 48](#).

Table 47: Disposition of relapses, ITT, study 307

Relapse category	Placebo N=42		SA 237 N=41	
	Number of relapses	% relapse-free	Number of relapses	% relapse-free
First Clinical Relapse during Double-Blind Treatment	27	35.7	18	56.1
CEC confirmation rate	70.4%		50%	
First CEC confirmed PDR during RCP (regardless of EDSS/FSS assessment limit of 7 days)	19	54.8	9	78.0
First CEC confirmed PDR with EDSS assessment performed within 7 days during Double-Blind Treatment	18	57.1	8	80.5

Source: TTE by PARAM by CNSR

Table 48: Disposition of relapses, anti-AQP4 IgG seropositive adults, study 307

Relapse category	Placebo N= 26		SA 237 N= 26	
	Number of relapses	% relapse-free	Number of relapses	% relapse-free
First Clinical Relapse during Double-Blind Treatment	17	34.6	11	57.7
CEC confirmation rate	70.6%		36.4%	
First CEC confirmed PDR during RCP (regardless of EDSS/FSS assessment limit of 7 days)	12	53.8	4	84.6
First CEC confirmed PDR with EDSS assessment performed within 7 days during Double-Blind Treatment	11	57.7	3	88.5

Source: AGEGR1_18 Subset of AQP4J_SEROPOS Subset of Join ADTTE 307 c ADSL 307 Ir by PARAM by CNSR.jmp

Reviewer Comment: The confirmation rate is higher for events occurring in the placebo group. The reason for this discrepancy is unclear. For example, for those events that were associated with a one point or greater increase on the EDSS, 13 of 14 in the placebo group were confirmed as relapses compared to 5 of 7 in the

satralizumab-mwge group, a fairly comparable proportion (Table 50). Of those for which the change in EDSS was less than 1, comparable proportions were confirmed. The same is the case for events with an increase of 2 or more points on one or more appropriate FSS scores (Table 51). A review of each of the 4 criteria for a clinically relevant new or worsening deficit (see 13.6) showed comparable confirmation rates for each for the two treatment groups.

Approximately 40% of the relapses were optic neuritis in the two treatment groups. The proportion declined slightly when the population was limited to anti-AQP4 IgG seropositive subjects and to anti-AQP4 IgG seropositive adult subjects (Table 49).

Table 49: Proportion of relapses that were optic neuritis, ITT, study 307

Population	PLACEBO		SA237	
	N	%	N	%
ITT	11	40.7%	8	40.0%
Anti-AQP4 antibody seropositive	7	36.8%	6	46.2%
Anti-AQP4 antibody seropositive Adults	6	35.3%	6	46.2%

Source: APERIOD_RCP Subset of ADRLP 307 TRT01P By (OPTNRFL); AQP4J_Seropos Subset of Join APERIODC_RCP of ADRLP c ADSL307lr TRT01P By (OPTNRFL); AGEGR1_18 Subset of AQP4J_Seropos Subset of Join APERIODC_RCP of ADRLP c ADSL307lr TRT01P By (OPTNRFL)

Table 50: Clinical events by EDSS increase of one or more, by relapse CEC confirmation, by treatment group, study 307

PDRE1*	RELAPSE	PLACEBO		SA237	
		N	%	N	%
N	N	9	31.0%	9	45.0%
N	Y	6	20.7%	4	20.0%
Y	N	1	3.4%	2	10.0%
Y	Y	13	44.8%	5	25.0%
	Total	29	100.0%	20	100.0%

Source: Join FDAPRLPcADSL TRT01P 307 TRT01P By (PDRE1, RELAPSE)

*: PDR1 = an increase of 1 or more points on the EDSS scale

Table 51: Clinical events by an increase of 2 or more on 1 or more FSS, by CEC confirmation, by treatment group, study 307

PDRF2X1*	RELAPSE	PLACEBO		SA237	
		N	%	N	%
N	N	8	27.6%	10	50.0%
N	Y	8	27.6%	2	10.0%

PDRF2X1*	RELAPSE	PLACEBO		SA237	
		N	%	N	%
Y	N	2	6.9%	1	5.0%
Y	Y	11	37.9%	7	35.0%
		29	100.0%	20	100.0%

Source: Join FDAPRLPcADSL TRT01P 307 TRT01P By (PDRF2X1, RELAPSE)

*: PDRF2X1 = an increase of at least 2 points on one or more appropriate FSS scores

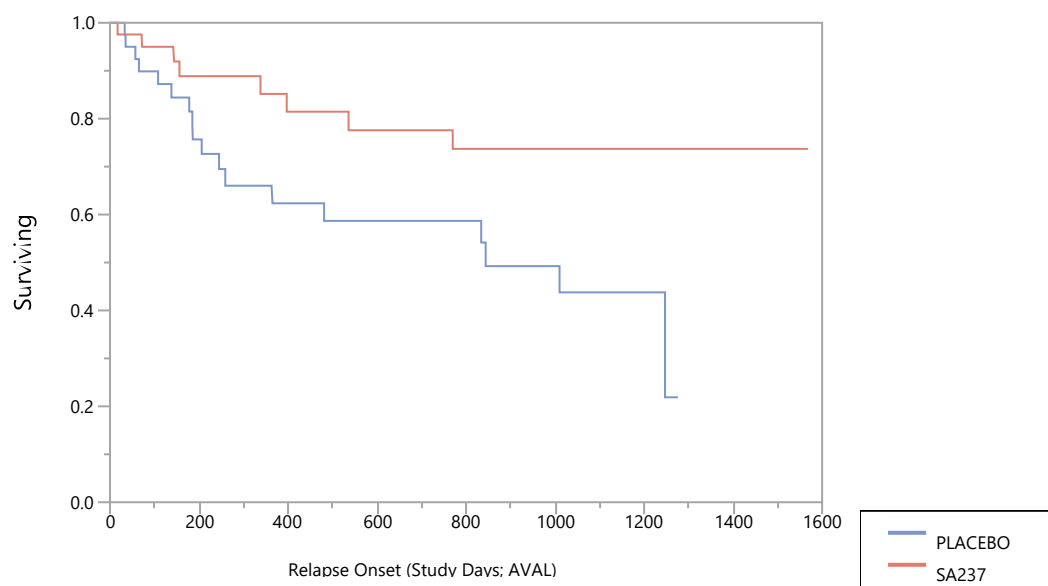
Efficacy Results – Primary Endpoint

The primary endpoint is the time to the first relapse confirmed by the Clinical Events Committee with an EDSS score determined within 7 days after the symptoms were reported to the site by the subject.

The analysis of the primary endpoint for the full ITT demonstrates a statistically significant delay in the time to the first CEC-confirmed relapse with EDSS/FSS evaluation within 7 days of the subject report with a hazard ratio of 0.38 (0.16, 0.88; $p = 0.0184$) as shown in [Figure 4](#). The results for the full ITT ([Table 52](#)), the anti-AQP4 IgG seronegative ([Table 53](#)), and the anti-AQP4 IgG seropositive ([Table 54](#)) subgroups indicate that there is no benefit for those who were seronegative.

Figure 4: Time to first CEC-confirmed relapse, ITT, study 307

Product-Limit Survival Fit Survival Plot



Time to event: AVAL

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Censored by CNSR
Censor Code 1
Grouped by TRT01P of ADTTE 307

Table 52: Summary, time to first CEC confirmed relapse, ITT, study 307

Group	Number failed	Number censored	Odds ratio	HR (sponsor)
PLACEBO	18	24	0.323 P = 0.0133*	0.38 (0.16, 0.88) p = 0.0184
SA237	8	33		
Combined	26	57		

Source: PDR01DB by TRT01P.jrp

*: Log-Rank

Table 53: Summary, time to first CEC confirmed relapse, anti-AQP4 IgG seronegative, ITT, study 307

Group	Number failed	Number censored	Odds ratio (reviewer)	HR (sponsor)
PLACEBO	6	8	0.741 p = 0.7579*	0.663 (0.197, 2.235) p = 0.5047
SA237	5	9		
Combined	11	17		

Source: PDR01DB by TRT01P group AQP4J.jrp

*: Log-Rank

Table 54: Summary, time to first CEC-confirmed relapse, anti-AQP4 IgG seropositive, ITT, study 307

Group	Number failed	Number censored	Odds ratio (reviewer)	HR (sponsor)
PLACEBO	12	16	0.167 P = 0.0052*	0.208 (0.058, 0.750) P = 0.0086
SA237	3	24		
Combined	15	40		

Source: PDR01DB by TRT01P group AQP4J.jrp

*: Log-Rank

Analysis of the primary endpoint for those subjects aged 18 years and older and who were seropositive for the anti-AQP4 IgG antibody is shown in [Figure 5](#) and summarized in [Table 55](#).

Figure 5: Time to first CEC-confirmed relapse, anti-AQP4 IgG seropositive adults, study 307

**Product-Limit Survival Fit
Survival Plot**

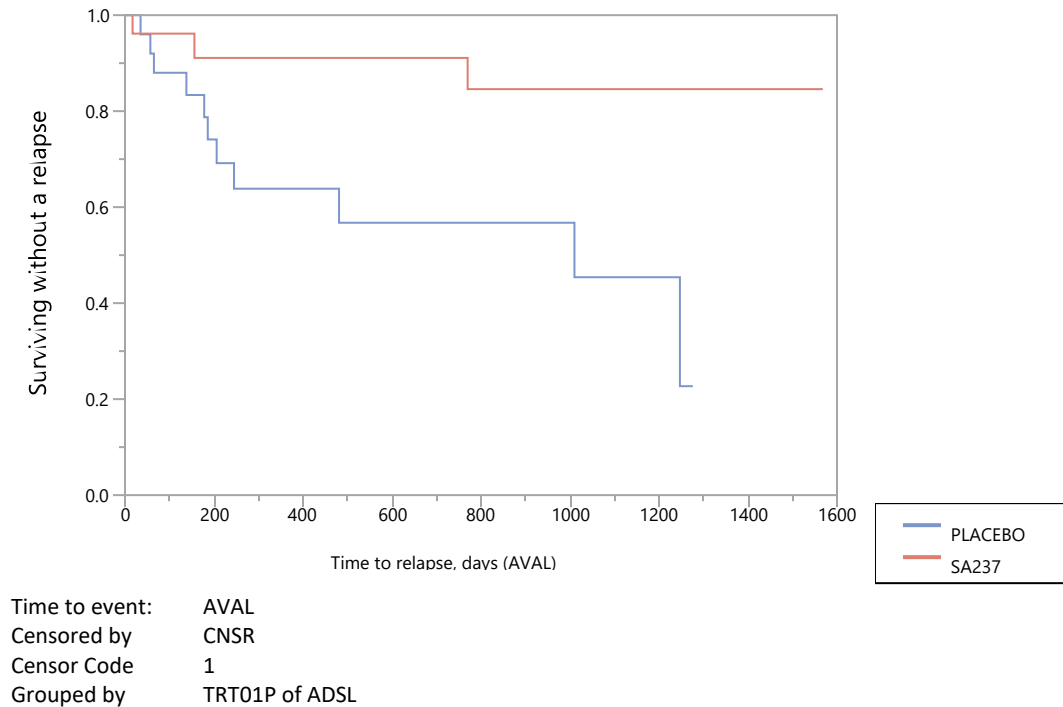


Table 55: Summary, time to first CEC-confirmed relapse, anti-AQP4 IgG seropositive adults, study 307

Group	Number failed	Number censored	Odds ratio	HR (sponsor)
PLACEBO	11	15	0.178 p = 0.0092*	
SA237	3	23		
Combined	14	38		

Source: PDR01DB POSADULTSbyTRT01P Survival.jrp

*: Log-Rank

Reviewer Comment: If all CEC-confirmed relapses are included, regardless of the 7-day limit to complete the EDSS assessment, the odds ratio for the AQP4+ subgroup would be 0.212, p=0.0152. If all Clinical Relapses, i.e. all relapses identified by the investigator, are included, the odds ratio for the AQP4+ subgroup would be 0.388, p=0.0995. If all Treated Relapses are included, the odds ratio for the AQP+ subgroup would be 0.458, p=0.1575.

Primary Endpoint by Subgroups

Analyses of the primary endpoint by various subgroups are listed in [Table 56](#). There is no indication of a benefit for patients who are seronegative for the anti-AQP4 IgG antibody.

Anti-AQP4 IgG serostatus: The data do not support a benefit for patients with NMOSD who are seronegative for the anti-AQP4 IgG antibody.

Pediatric age group: There are too few subjects below the age of 18 to make valid conclusions regarding efficacy. Of the 7 subjects in this group, only 3 were seropositive, two of whom were randomized to placebo and one to satralizumab-mwge. One placebo and one satralizumab-mwge subject had a primary endpoint event.

Reviewer Comment: Because of the subgroup analyses by anti-AQP4 IgG serostatus and the results for the 7 subjects less than 18 years old, analyses for the seropositive adult population are listed.

Sex: The ITT population was predominantly female, and the seropositive adult population was all female. For the ITT, 1 of the 2 male placebo subjects and 2 of 4 male satralizumab-mwge subjects had a primary endpoint event.

Age less than 50 vs. 50 and over (reviewer analysis): Approximately 45% of subjects were 50 years old or greater. Efficacy appears to be significant in those over and under 50 years old.

Concurrent therapy for NMOSD relapse prevention: Concurrent therapy for relapse prevention was allowed in study 307. Where there are a number of subjects sufficient to draw tentative conclusions regarding efficacy, the odds and hazard ratios support a benefit with concurrent azathioprine and oral corticosteroids although the result is nominally significant in the oral corticosteroid group only.

Region: The result was not statistically significant for the EU/other region subgroup, but the OR and HR did support a benefit.

Race: The evidence of benefit is clear for Japanese and non-Japanese Asian subgroup. The OR supports a benefit in the non-Asian sub-population.

Baseline EDSS: The benefit is nominally significant for those with a baseline EDSS of 5 or less. For the small group with a baseline EDSS over 5, the OR supports a benefit.

Baseline ARR: The HR and OR support a benefit for those with a baseline ARR of one or more than one although nominal significance was seen only for seropositive adults with a baseline ARR of 1.

Reviewer Comment: The overall evidence of benefit is positive for nearly all subgroups with the exception of those who were seronegative and for those who were less than 18 years old.

Table 56: Analyses of the primary endpoint by subgroups, study 307

Subgroup	ITT				Anti-AQP4 IgG seropositive adults			
	N	OR*, p-value**	HR, 95%CI	p-value	N	OR*, p-value**	HR***, 95%CI	p-value****
AQP4 IgG								
Negative	28	0.741 p = 0.7579	0.663 (0.197, 2.235)	0.5047				
Positive	55	0.167 p= 0.0052	0.208 (0.058, 0.750)	0.0086	52			
Age								
≥18	76	0.302 p=0.0129	0.362 (0.149, 0.878)	0.0192	52	0.178 p=0.0092	0.223 (0.061, 0.819)	0.0143
<18	7	0.6 p=0.6171	0.0 (0.0, NE)	0.1573				
SEX								

Subgroup	ITT				Anti-AQP4 IgG seropositive adults			
	N	OR*, p-value**	HR, 95%CI	p-value	N	OR*, p-value**	HR***, 95%CI	p-value****
Female	77	0.262 p=0.0055			52	0.178 p=0.0092	0.223 (0.061, 0.819)	0.0143
Male	6	1.00 p=0.5019						
Age								
<50	55	0.431 p=0.0919			30	0.219 p=0.0497	0.114 (0.012, 1.130)	0.0398
≥50	28	0.00 p=0.0346			22	0.00 p=0.100	0.00 (0.00, NE)	0.1823
Baseline therapy								
AZA ¹	29	0.390 P=0.2286	0.621 (0.188, 2.051)	0.4307	22	0.313 P=0.2780	0.669 (0.136, 3.293)	0.6198
Myco ²	12	1.00 P=0.7317	0.00 (0.00, NE)	0.1025	3	0.00	NE	NE
OCS ³	37	0.094 P=0.0114	0.152 (0.018, 1.253)	0.0462	27	0.00 P=0.0056	0.000 (0.000, NE)	0.0134
Region								
Asia	34	0.105 p=0.0308	0.150 (0.018, 1.231)	p=0.0419	26	0.0 p=0.0036	0.00 (0.00, NE)	0.0045
EU/other	49	0.460 p=0.1317	0.495 (0.191, 1.283)	p=0.1400	26	0.675 p=0.4701	0.628 (0.132, 2.995)	0.5565
RACE								
White	45	0.452 p=0.1406			24	0.667 p=0.4201	0.586 (0.125, 2.734)	0.4919
Asian ⁴	38	0.102 p=0.0289			27	0.0 p=0.0033	0.00 (0.00, NE)	0.0045
Baseline EDSS								
≤5	67	0.308			38	0.088	0.119	0.0195

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Subgroup	ITT				Anti-AQP4 IgG seropositive adults			
	N	OR*, p-value**	HR, 95%CI	p-value	N	OR*, p-value**	HR***, 95%CI	p-value****
		p=0.0235				p=0.0063	(0.014, 0.986)	
>5	15	0.286 p=0.2404			13	0.222 p=0.2971	0.00 (0.00, NE)	0.0833
Baseline ARR (ARRGR1)								
1	40	0.265 p=0.1038	0.354 (0.094, 1.341)	P=0.1105	29	0.0 p=0.0123	0.00 (0.00, NE)	0.0131
>1	43	0.375 p=0.0725	0.396 (0.134, 1.167)	P=0.0823	23	0.583 p=0.2308	0.478 (0.104, 2.195)	0.3332

*: Reviewer unadjusted odds ratio

**: Log-Rank from Kaplan-Meier model

***: sponsor calculation

****: Cox proportional hazards model stratified for baseline ARR and geographic region

1: Azathioprine alone

2: Mycophenolate alone

3: Oral corticosteroids alone

4: Japanese and non-Japanese Asian

Data Quality and Integrity

There was a concern regarding access to the database after the “interim” database lock. The “interim” lock was for the primary analyses reported in the application. The database remained locked for all additional data collected, i.e. during the OLE. The sponsor provided a listing of all access to the database of both studies 309 and 307 up to and after the interim database lock. The sponsor reported that “The database on which the primary analysis for the BLA is based was not unlocked after the initial ‘interim’ lock”.

The sponsor was asked to detail the process of EDSS determination for the purpose of identifying relapses. Some changes were made to these EDSS scores in response to queries from the CRO that had responsibility for this process. It appears that none were made spontaneously by the site. Once the final data was sent to the CEC, there were subsequent changes made. However, the CEC reported by email that no changes to the adjudication decision were made due to these changes.

Efficacy Results – Secondary and other relevant endpoints

Change in Visual Analogue Scale for Pain from Baseline to Week 24

There was no significant improvement on the VAS analogue pain scale at Week 24 ([Table 57](#)).

Table 57: VAS, change at Week 24, RCP, study 307

TRT01P	N	Change in VAS		
		Mean	Std Dev	Median
PLACEBO	29	-5.9	18.1	-3
SA237	29	4.14	18.6	0

Source: AVISIT_WK24 Subset of PARAM_VASMM Subset of EPOCH_RCP Subset of ADVAS 307 CHG By (TRT01P).jmp

Reviewer Comment: Similar to the result in study 309, there was more of an improvement in the placebo group.

Change in FACIT fatigue scale score from baseline at week 24

There was no significant improvement in fatigue at week 24 as measured by the FACIT total score ([Table 58](#)).

Table 58: Change in FACIT total score at week 24, RCP, study 307

TRT01P	N	Change in FACIT total score		
		Mean	Std Dev	Median
PLACEBO	29	3.48	6.56	3
SA237	29	0.34	8.07	0

Source: AVISIT_WK24 Subset of QSTEST_TOTAL Subset of QSCAT_FACIT Subset of EPOCH_RCP Subset of ADFACIT 307 CHG By (TRT01P).jmp

Relapse-free

At the end of the RCP, 88.5% of subjects treated with satralizumab-mwge remained free of a relapse compared to 57.7% of the placebo group ([Table 59](#)).

Table 59: Proportion relapse-free at end of RCT, anti-AQP4 positive adults, study 307

Relapse	N	Placebo		SA 237	
		N	%	N	%
Yes	14	11	42.3	3	11.5
No	38	15	57.7	23	88.5

Source: PDR01DB Subset of AGEGR1 18andover Subset of AQP4J_SEROPOS Subset of Join ADTTE 307 c ADSL 307 Ir TRT01P By (CNSR).jmp

Reviewer Comment: The sponsor provided the above analysis in response to an AIR. The number of subjects who were relapse-free is the same as in the above table with an HR of 0.22 (0.06, 0.82), p=0.0143.

Dose/Dose Response

Dose response was not studied.

Durability of Response

The durability of the response was not studied.

Persistence of Effect

The persistence of efficacy was not studied

Additional Analyses Conducted on the Individual Trial

There were no additional efficacy analyses.

7 Integrated Review of Effectiveness

7.2 Assessment of Efficacy Across Trials

Studies 307 and 309 differ primarily by the use of concurrent immunotherapies in study 307 that were not allowed in study 309. Therefore, for most analyses, it is not appropriate to pool these studies for efficacy.

7.2.1 Primary Endpoints

The primary efficacy endpoint for the two studies and the key subgroups based on anti-AQP4 antibody status and the adult subgroup for study 307 are shown in [Table 60](#). The effect size for subjects who were anti-AQP4 antibody seropositive is very similar for the two groups, as is the lack of a benefit for those who were anti-AQP4 antibody seronegative.

Table 60: Summary of primary endpoint analyses, studies 307 and 309

	307			309		
	N	HR	P	N	HR	P
ITT	83	0.38 (0.16, 0.88)	0.0184	95	0.450 (0.23, 0.89)	0.0184
AQP4pos	55	0.208 (0.058, 0.750)	0.0086	64	0.261 (0.108, 0.627)	0.0014
AQP4neg	28	0.663 (0.197, 2.235)	0.5047	31	1.192 (0.298, 4.775)	0.8036
AQP4pos adults	52			64	0.261 (0.108, 0.627)	0.0014

7.2.2 Secondary and Other Endpoints

The secondary endpoints were not pooled. No benefit was seen on the VAS pain measure or on the FACIT fatigue score in either study.

7.2.3 Subpopulations

The analyses were not pooled for any of the subgroups.

7.2.4 Dose and Dose-Response

One dose was studied.

7.2.5 Onset, Duration, and Durability of Efficacy Effects

Duration and durability were not studied

7.3 Additional Efficacy Considerations

7.3.1 Considerations on Benefit in the Postmarket Setting

The population for approval will be limited to adult patients with NMOSD who are anti-AQP4 antibody seropositive. It is not clear whether these patients will be treated with Enspryng alone or in combination with other immunotherapies. Study 307 provides limited data that the benefit is not altered by the concurrent use of corticosteroids. The number of subjects on concurrent azathioprine and mycophenolate in study 307 was too small to assess their impact on efficacy.

7.3.2 Other Relevant Benefits

No benefits, other than the benefit on relapses, were demonstrated.

7.4 Integrated Assessment of Effectiveness

The data demonstrate in two adequate and well controlled trials

8 Review of Safety

8.2 Safety Review Approach

For most analysis, because of the concurrent use of immunosuppressant drugs in study 307, each study was analyzed separately.

8.3 Review of the Safety Database

8.3.1 Overall Exposure

The extent of exposure in the studies of NMOSD, and in a single ascending dose study in healthy volunteers (SA-001JP) and a multiple ascending dose study in patients with rheumatoid arthritis (SA-105JP) is shown in [Table 61](#). There are 132 subjects with exposure to satralizumab-mwge of over one year ([Table 62](#)). The median duration of exposure at the time of the safety update was 2.5 years ([Table 63](#)).

Reviewer Comment: There are over 100 subjects exposed for one year or more to satralizumab-mwge at the proposed dose for marketing, meeting the minimum ICH standard. The total number of subjects exposed is below the standard. Continued safety surveillance will be important.

Table 61: Overall exposure, ISS

Study	N		Exposure (patient-years)	
	SA237	Placebo	SA237	Placebo
Studies in NMOSD				
Study 307	26	26	49.347	28.679
Study 309	23	41	77.101	24.564
Any SA237*	166		431.6	
PK/safety studies				
SA-001JP	72	12	Single dose study	
SA-105JP**	33	0	31.9**	0

*: as of the 90-day safety update

**: all dose levels combined

Table 62: Duration of exposure to SA237, years, all treated population

Distribution of AP04TRTDURYRS*	N Rows
0 to <1	34
1 to <2	20
2 to <3	44
3 to <4	31
4 to <5	35
5 to <6	2

Source: APTFL_Y Subset of ADSL safety update pooled By (Distribution of AP04TRTDURYRS).jmp

*: reviewer data field derived

Table 63: Duration of exposure to SA237, years, summary, all treated population

N Rows	AP04 (SA237 treatment period) years				
	Mean	Std Dev	Min	Max	Median
166	2.6	1.4	0.2	5.3	2.5

Source: Summary of AP04 duration years APTFL_Y Subset of ADSL safety update pooled lr.jmp

8.3.2 Relevant characteristics of the safety population:

The safety and ITT populations are the same. The demographic characteristics are listed in [Table 8](#) and [Table 9](#) for study 309 and in [Table 34](#) and [Table 35](#) for study 307.

8.3.3 Adequacy of the safety database:

The safety database was adequate.

8.4 Adequacy of Applicant's Clinical Safety Assessments

8.4.1 Issues Regarding Data Integrity and Submission Quality

See the comment on data integrity for the individual studies.

8.4.2 Categorization of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA), version 16.1 was used to categorize adverse events.

8.4.3 Routine Clinical Tests

Routine safety laboratory assessments included a Complete Blood Count, Chemistries, urinalysis, electrocardiogram, and pregnancy test where appropriate. In addition, complement levels were assessed periodically.

8.5 Safety Results

8.5.1 Deaths

Study 309

There were no deaths during the RCP in either treatment group

Study 307

There were no deaths during the RCP in either treatment group

8.5.2 Serious Adverse Events

Study 309

The incidence of any SAE during the RCP for the full ITT was 15.6% for the placebo group and 19.0% for the satralizumab-mwge group ([Table 64](#)) and for anti-AQP4 IgG seropositive adults the incidence was 13.0% for the placebo group and 17.1% for the satralizumab-mwge group ([Table 65](#)). SAEs by preferred term are listed by the most frequent for the ITT in [Table 66](#) and for anti-AQP4 IgG seropositive adults in [Table 67](#). There were no clear imbalances between the treatment groups for a specific SOC or AE preferred term.

Reviewer Comment: The relatively low number of subjects exposed to satralizumab-mwge limits interpretation of the SAE's. As might be expected, infections are the most common category but are no more frequent than in the

placebo group. Unlike study 307, there are no concurrent immunosuppressant therapies that confound the results in study 309.

Table 64: Serious adverse events by SOC, ITT, study 309

AEBODSYS	PLACEBO	SA237
Infections and infestations	3 (9.4%)	6 (9.5%)
Psychiatric disorders	0 (0.0%)	2 (3.2%)
Cardiac disorders	0 (0.0%)	2 (3.2%)
Injury, poisoning and procedural complications	0 (0.0%)	2 (3.2%)
Gastrointestinal disorders	0 (0.0%)	2 (3.2%)
General disorders and administration site conditions	0 (0.0%)	2 (3.2%)
Respiratory, thoracic and mediastinal disorders	0 (0.0%)	2 (3.2%)
Eye disorders	0 (0.0%)	1 (1.6%)
Nervous system disorders	2 (6.3%)	0 (0.0%)
Subjects(filtered)	5 (15.6%)	12 (19.0%)
1stCollItemSubjects	32 (100.0%)	63 (100.0%)

Source: JRevSelADSLSAFFL_Y SOCbyADSLTRT01AfiltEPOCH_RCP AESER_Y

Table 65: Serious adverse events by SOC, anti-AQP4 IgG seropositive adults, study 309

AEBODSYS	PLACEBO	SA237
Infections and infestations	1 (4.3%)	4 (9.8%)
Psychiatric disorders	0 (0.0%)	2 (4.9%)
Injury, poisoning and procedural complications	0 (0.0%)	2 (4.9%)
Respiratory, thoracic and mediastinal disorders	0 (0.0%)	2 (4.9%)
General disorders and administration site conditions	0 (0.0%)	1 (2.4%)
Eye disorders	0 (0.0%)	1 (2.4%)
Cardiac disorders	0 (0.0%)	1 (2.4%)
Nervous system disorders	2 (8.7%)	0 (0.0%)
Subjects(filtered)	3 (13.0%)	7 (17.1%)
1stCollItemSubjects	23 (100.0%)	41 (100.0%)

Source: JRevSelADSLSAFFL_Y AQP4J_POS SOCbyADSLTRT01AfiltEPOCH_RCP AESER_Y

Table 66: Serious adverse events by preferred term, ITT, study 309

Dictionary Derived Term	PLACEBO	SA237
Mental status changes	0 (0.0%)	2 (3.2%)
Influenza	0 (0.0%)	2 (3.2%)
Radius fracture	0 (0.0%)	1 (1.6%)
Pyelonephritis	0 (0.0%)	1 (1.6%)
Pulmonary sepsis	0 (0.0%)	1 (1.6%)
Urosepsis	0 (0.0%)	1 (1.6%)
Apnoea	0 (0.0%)	1 (1.6%)
Bradycardia	0 (0.0%)	1 (1.6%)
Enterocolitis	0 (0.0%)	1 (1.6%)
Hypothermia	0 (0.0%)	1 (1.6%)
Acute myocardial infarction	0 (0.0%)	1 (1.6%)

Dictionary Derived Term	PLACEBO	SA237
Visual impairment	0 (0.0%)	1 (1.6%)
Injury	0 (0.0%)	1 (1.6%)
Nausea	0 (0.0%)	1 (1.6%)
Non-cardiac chest pain	0 (0.0%)	1 (1.6%)
Pneumonia	0 (0.0%)	1 (1.6%)
Pulmonary oedema	0 (0.0%)	1 (1.6%)
Upper respiratory tract infection	1 (3.1%)	0 (0.0%)
Neuromyelitis optica	1 (3.1%)	0 (0.0%)
Cystitis	1 (3.1%)	0 (0.0%)
Cervical radiculopathy	1 (3.1%)	0 (0.0%)
Urinary tract infection	1 (3.1%)	0 (0.0%)
Subjects(filtered)	5 (15.6%)	12 (19.0%)
1stCollItemSubjects	32 (100.0%)	63 (100.0%)

Source: JRev309SelADSLSAFFL_Y AEDECODbyTRT01A TRTEMFL_Y PERIOD_RCP AESER_Y

Table 67: Serious adverse events by preferred term, anti-AQP4 IgG seropositive adults, study 309

AEDECOD	PLACEBO	SA237
Mental status changes	0 (0.0%)	2 (4.9%)
Urosepsis	0 (0.0%)	1 (2.4%)
Radius fracture	0 (0.0%)	1 (2.4%)
Apnoea	0 (0.0%)	1 (2.4%)
Bradycardia	0 (0.0%)	1 (2.4%)
Hypothermia	0 (0.0%)	1 (2.4%)
Influenza	0 (0.0%)	1 (2.4%)
Visual impairment	0 (0.0%)	1 (2.4%)
Injury	0 (0.0%)	1 (2.4%)
Pulmonary oedema	0 (0.0%)	1 (2.4%)
Pulmonary sepsis	0 (0.0%)	1 (2.4%)
Pyelonephritis	0 (0.0%)	1 (2.4%)
Neuromyelitis optica	1 (4.3%)	0 (0.0%)
Cervical radiculopathy	1 (4.3%)	0 (0.0%)
Upper respiratory tract infection	1 (4.3%)	0 (0.0%)
Subjects(filtered)	3 (13.0%)	7 (17.1%)
1stCollItemSubjects	23 (100.0%)	41 (100.0%)

Source: JRevSelADSLSAFFL_Y AQP4J_POS AEDECODbyADSLTRT01AfiltePOCH_RCP AESER_Y

Study 307

The incidence of any SAE during the RCP was 21.4% in the placebo group and 17.1% in the satralizumab-mwge group for the full ITT ([Table 68](#)) and 26.9% for both treatment group for anti-AQP4 IgG seropositive adults ([Table 69](#)). SAEs by preferred term are listed by the most frequent for the ITT in [Table 70](#) and for anti-AQP4 IgG seropositive adults in [Table 71](#). There is no notable imbalance between treatment groups for a specific SOC or preferred term. No single

event term raises a serious concern.

Reviewer Comment: interpretation of the safety data in study 307 is limited by the small number of subjects and also by the concurrent use of immunosuppressant drugs in the comparator group.

Table 68: Serious adverse events by SOC and preferred term, during RCP, ITT, study 307

AESOC	AEDECOD	PLACEBO	SA237
Blood and lymphatic system disorders	Anaemia macrocytic	0 (0.0%)	1 (2.4%)
	Autoimmune thrombocytopenia	1 (2.4%)	0 (0.0%)
	Leukopenia	1 (2.4%)	0 (0.0%)
	Lymphopenia	1 (2.4%)	0 (0.0%)
Eye disorders	Retinal vein thrombosis	1 (2.4%)	0 (0.0%)
Gastrointestinal disorders	Abdominal pain	1 (2.4%)	0 (0.0%)
Infections and infestations	Appendicitis	1 (2.4%)	0 (0.0%)
	Escherichia sepsis	1 (2.4%)	0 (0.0%)
	Pneumonia	0 (0.0%)	1 (2.4%)
	Urinary tract infection	1 (2.4%)	1 (2.4%)
Injury, poisoning and procedural complications	Femur fracture	0 (0.0%)	1 (2.4%)
	Spinal compression fracture	0 (0.0%)	1 (2.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast cancer	1 (2.4%)	0 (0.0%)
	Hepatic cancer	1 (2.4%)	0 (0.0%)
Nervous system disorders	Tension headache	0 (0.0%)	1 (2.4%)
Psychiatric disorders	Suicide attempt	0 (0.0%)	1 (2.4%)
Renal and urinary disorders	Dysuria	1 (2.4%)	0 (0.0%)
Reproductive system and breast disorders	Cervical dysplasia	0 (0.0%)	1 (2.4%)
	Uterine polyp	1 (2.4%)	0 (0.0%)
Subtotal	Subjects(filtered)	9 (21.4%)	7 (17.1%)
Total	1stCollItemSubjects	42 (100.0%)	41 (100.0%)

Source: JRevSelSAFFL_Y AESOCbyAEDECODbyADSLTRT01AbyADAETRT01AfiltAESER_Y EPOCH_RCP

Table 69: Serious adverse events by SOC and PT, during RCP, anti-AQP4 IgG seropositive adults, study 307

AESOC	AEDECOD	PLACEBO	SA237
Blood and lymphatic system disorders	Anaemia macrocytic	0 (0.0%)	1 (3.8%)
	Autoimmune thrombocytopenia	1 (3.8%)	0 (0.0%)
	Leukopenia	1 (3.8%)	0 (0.0%)
	Lymphopenia	1 (3.8%)	0 (0.0%)
Gastrointestinal disorders	Abdominal pain	1 (3.8%)	0 (0.0%)
Infections and infestations	Appendicitis	1 (3.8%)	0 (0.0%)
	Escherichia sepsis	1 (3.8%)	0 (0.0%)
	Pneumonia	0 (0.0%)	1 (3.8%)
	Urinary tract infection	1 (3.8%)	1 (3.8%)

AESOC	AEDECOD	PLACEBO	SA237
Injury, poisoning and procedural complications	Femur fracture	0 (0.0%)	1 (3.8%)
	Spinal compression fracture	0 (0.0%)	1 (3.8%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Hepatic cancer	1 (3.8%)	0 (0.0%)
Nervous system disorders	Tension headache	0 (0.0%)	1 (3.8%)
Psychiatric disorders	Suicide attempt	0 (0.0%)	1 (3.8%)
Renal and urinary disorders	Dysuria	1 (3.8%)	0 (0.0%)
Reproductive system and breast disorders	Cervical dysplasia	0 (0.0%)	1 (3.8%)
	Uterine polyp	1 (3.8%)	0 (0.0%)
Subtotal	Subjects(filtered)	7 (26.9%)	7 (26.9%)
Total	1stCollItemSubjects	26 (100.0%)	26 (100.0%)

Source: JRevSelSAFFL_Y AQP4J_POS AGEGR1_18 AESOCbyAEDECODbyADSLTRT01AbyADAETRT01AfilAESER_Y EPOCH_RCP

Table 70: Serious adverse events by PT, during RCT, ITT, study 307

AEDECOD	PLACEBO	SA237
Tension headache	0 (0.0%)	1 (2.4%)
Spinal compression fracture	0 (0.0%)	1 (2.4%)
Pneumonia	0 (0.0%)	1 (2.4%)
Femur fracture	0 (0.0%)	1 (2.4%)
Cervical dysplasia	0 (0.0%)	1 (2.4%)
Anaemia macrocytic	0 (0.0%)	1 (2.4%)
Suicide attempt	0 (0.0%)	1 (2.4%)
Urinary tract infection	1 (2.4%)	1 (2.4%)
Hepatic cancer	1 (2.4%)	0 (0.0%)
Lymphopenia	1 (2.4%)	0 (0.0%)
Leukopenia	1 (2.4%)	0 (0.0%)
Uterine polyp	1 (2.4%)	0 (0.0%)
Escherichia sepsis	1 (2.4%)	0 (0.0%)
Dysuria	1 (2.4%)	0 (0.0%)
Breast cancer	1 (2.4%)	0 (0.0%)
Autoimmune thrombocytopenia	1 (2.4%)	0 (0.0%)
Appendicitis	1 (2.4%)	0 (0.0%)
Retinal vein thrombosis	1 (2.4%)	0 (0.0%)
Abdominal pain	1 (2.4%)	0 (0.0%)
Subjects(filtered)	9 (21.4%)	7 (17.1%)
1stCollItemSubjects	42 (100.0%)	41 (100.0%)

Source: JRevSelADSLSAFFL_Y AEDECODbyADSLTRT01AbyADAETRT01AfilAESER_Y EPOCH_RCP

Table 71: Serious adverse events by PT, during RCT, anti-AQP4 IgG seropositive adults, study 307

AEDECOD	PLACEBO	SA237
Suicide attempt	0 (0.0%)	1 (3.8%)
Spinal compression fracture	0 (0.0%)	1 (3.8%)
Pneumonia	0 (0.0%)	1 (3.8%)

AEDECOD	PLACEBO	SA237
Femur fracture	0 (0.0%)	1 (3.8%)
Cervical dysplasia	0 (0.0%)	1 (3.8%)
Anaemia macrocytic	0 (0.0%)	1 (3.8%)
Tension headache	0 (0.0%)	1 (3.8%)
Urinary tract infection	1 (3.8%)	1 (3.8%)
Lymphopenia	1 (3.8%)	0 (0.0%)
Uterine polyp	1 (3.8%)	0 (0.0%)
Leukopenia	1 (3.8%)	0 (0.0%)
Hepatic cancer	1 (3.8%)	0 (0.0%)
Escherichia sepsis	1 (3.8%)	0 (0.0%)
Dysuria	1 (3.8%)	0 (0.0%)
Autoimmune thrombocytopenia	1 (3.8%)	0 (0.0%)
Appendicitis	1 (3.8%)	0 (0.0%)
Abdominal pain	1 (3.8%)	0 (0.0%)
Subjects(filtered)	7 (26.9%)	7 (26.9%)
1stCollItemSubjects	26 (100.0%)	26 (100.0%)

Source: JRevSelADSLSAFFL_Y AQP4J_POS AGEGR1_18 AEDECODbyADSLTRT01AbyADAETRT01AfiltAESER_Y EPOCH_RCP

8.5.3 Dropouts and/or Discontinuations Due to Adverse Effects

Study 309

In the ITT, study treatment was discontinued due to an AE of Systemic lupus erythematosus (SLE) in one subject in the placebo group and in one subject due to an AE of pneumonia in the satralizumab-mwge group. The anti-AQP4 IgG seropositive population only included the AE of SLE.

Study 307

An adverse event that led to discontinuation of treatment (DAE) occurred in 4 subjects (9.5%) treated with placebo and in 3 subjects (7.3%) treated with satralizumab-mwge ([Table 72](#)). The terms for these events in the satralizumab-mwge group included one related to a low neutrophil count, 2 related to liver transaminases and one suggesting an allergic reaction. [Table 73](#) lists the DAEs for the AQP4 IgG seropositive adult population.

Table 72: Adverse events causing discontinuation of treatment, ITT, study 307

AEDECOD	PLACEBO	SA237
Neutrophil count decreased	0 (0.0%)	1 (2.4%)
Aspartate aminotransferase increased	0 (0.0%)	1 (2.4%)
Alanine aminotransferase increased	0 (0.0%)	1 (2.4%)
Urticaria	0 (0.0%)	1 (2.4%)
Lymphopenia	1 (2.4%)	0 (0.0%)
Hepatic cancer	1 (2.4%)	0 (0.0%)

AEDECOD	PLACEBO	SA237
Breast cancer	1 (2.4%)	0 (0.0%)
Autoimmune thrombocytopenia	1 (2.4%)	0 (0.0%)
Subjects(filtered)	4 (9.5%)	3 (7.3%)
1stCollItemSubjects	42 (100.0%)	41 (100.0%)

Source: JRevSelADSLSAFFL_Y AEDECODbyADSLTRT01AfiltePOCH_RCP AEACN_WD

Table 73: Adverse events causing discontinuation of treatment, anti-AQP4 IgG seropositive adults, study 307

AEDECOD	PLACEBO	SA237
Neutrophil count decreased	0 (0.0%)	1 (3.8%)
Aspartate aminotransferase increased	0 (0.0%)	1 (3.8%)
Alanine aminotransferase increased	0 (0.0%)	1 (3.8%)
Urticaria	0 (0.0%)	1 (3.8%)
Lymphopenia	1 (3.8%)	0 (0.0%)
Hepatic cancer	1 (3.8%)	0 (0.0%)
Autoimmune thrombocytopenia	1 (3.8%)	0 (0.0%)
Subjects(filtered)	3 (11.5%)	3 (11.5%)
1stCollItemSubjects	26 (100.0%)	26 (100.0%)

Source: JRevSelADSLSAFFL_Y AQP4J_POS AGEGR1_18 AEDECODbyADSLTRT01AfiltePOCH_RCP AEACN_WD

8.5.4 Significant Adverse Events

8.5.5 Treatment Emergent Adverse Events and Adverse Reactions

Study 309

At least one AE occurred in 75% of placebo and 92.1% of satralizumab-mwge subjects in the full ITT (Table 74) and in 69.6% of placebo subjects and 87.8% of satralizumab-mwge subjects who were anti-AQP4 seropositive adults (Table 75). AEs in the Infections SOC were the most common for both treatment groups. There were several SOCs in which AEs were notably more common in the satralizumab-mwge treatment group, including Musculoskeletal and Connective Tissue Disorders, Blood and Lymphatic System Disorders, and Cardiac Disorders.

Reviewer Comment: The most prominent preferred term from the Musculoskeletal and Connective Tissue disorders SOC is arthralgia, although there are a number of other terms that all suggest generalized muscle and skeletal discomfort (Table 76).

White cell cytopenias account for the majority of the terms in the Blood and Lymphatic Disorders SOC that account for the increased proportion of satralizumab-mwge subjects in this SOC (Table 77). The Narrow SMQ for Haematopoietic leukopenia yields an odds ratio of 2.188 (0.609, 9.878, p= 0.279).

This safety signal is also noted in study 307 (see [Table 83](#) and related discussion).

The AE terms in the Cardiac SOC do not suggest a significant safety concern.

Table 74: Adverse events by SOC, ITT, study 309

Body System or Organ Class	PLACEBO	SA237
Infections and infestations	14 (43.8%)	34 (54.0%)
Gastrointestinal disorders	13 (40.6%)	26 (41.3%)
Musculoskeletal and connective tissue disorders	6 (18.8%)	31 (49.2%)
Nervous system disorders	11 (34.4%)	18 (28.6%)
General disorders and administration site conditions	7 (21.9%)	19 (30.2%)
Skin and subcutaneous tissue disorders	4 (12.5%)	20 (31.7%)
Injury, poisoning and procedural complications	8 (25.0%)	16 (25.4%)
Investigations	8 (25.0%)	15 (23.8%)
Respiratory, thoracic and mediastinal disorders	6 (18.8%)	16 (25.4%)
Blood and lymphatic system disorders	3 (9.4%)	16 (25.4%)
Psychiatric disorders	4 (12.5%)	13 (20.6%)
Eye disorders	2 (6.3%)	11 (17.5%)
Renal and urinary disorders	3 (9.4%)	9 (14.3%)
Metabolism and nutrition disorders	3 (9.4%)	8 (12.7%)
Cardiac disorders	0 (0.0%)	5 (7.9%)
Ear and labyrinth disorders	1 (3.1%)	4 (6.3%)
Reproductive system and breast disorders	2 (6.3%)	3 (4.8%)
Immune system disorders	3 (9.4%)	2 (3.2%)
Vascular disorders	0 (0.0%)	3 (4.8%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (3.1%)	2 (3.2%)
Hepatobiliary disorders	0 (0.0%)	1 (1.6%)
Subjects(filtered)	24 (75.0%)	58 (92.1%)
1stColltemSubjects	32 (100.0%)	63 (100.0%)

Source: JRev309SeIADSLSAFFL_Y SOCbyTRT01AfilTRTEMFL_Y PERIOD_RCP

Table 75: Adverse events by SOC, anti-AQP4 IgG seropositive adults, study 309

AEBODSYS	PLACEBO	SA237
Infections and infestations	10 (43.5%)	22 (53.7%)
Musculoskeletal and connective tissue disorders	4 (17.4%)	21 (51.2%)
Gastrointestinal disorders	11 (47.8%)	16 (39.0%)
Skin and subcutaneous tissue disorders	2 (8.7%)	15 (36.6%)
General disorders and administration site conditions	4 (17.4%)	13 (31.7%)
Blood and lymphatic system disorders	3 (13.0%)	13 (31.7%)
Injury, poisoning and procedural complications	4 (17.4%)	12 (29.3%)
Investigations	6 (26.1%)	12 (29.3%)
Respiratory, thoracic and mediastinal disorders	3 (13.0%)	11 (26.8%)
Eye disorders	1 (4.3%)	9 (22.0%)
Nervous system disorders	7 (30.4%)	9 (22.0%)
Psychiatric disorders	2 (8.7%)	8 (19.5%)

AEBODSYS	PLACEBO	SA237
Renal and urinary disorders	3 (13.0%)	6 (14.6%)
Metabolism and nutrition disorders	3 (13.0%)	5 (12.2%)
Ear and labyrinth disorders	1 (4.3%)	3 (7.3%)
Cardiac disorders	0 (0.0%)	3 (7.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0%)	2 (4.9%)
Immune system disorders	1 (4.3%)	2 (4.9%)
Vascular disorders	0 (0.0%)	2 (4.9%)
Reproductive system and breast disorders	1 (4.3%)	1 (2.4%)
Hepatobiliary disorders	0 (0.0%)	1 (2.4%)
Subjects(filtered)	16 (69.6%)	36 (87.8%)
1stCollItemSubjects	23 (100.0%)	41 (100.0%)

Source: JRevSelADSLSAFFL_Y AQP4J_POS SOCbyADSLTRT01AfilTEPOCH_RCP

Table 76: Adverse events, ITT, Musculoskeletal and Connective Tissue Disorders, study 309

Dictionary Derived Term	PLACEBO	SA237
Arthralgia	1 (3.1%)	10 (15.9%)
Pain in extremity	3 (9.4%)	9 (14.3%)
Back pain	3 (9.4%)	4 (6.3%)
Musculoskeletal pain	2 (6.3%)	4 (6.3%)
Musculoskeletal stiffness	0 (0.0%)	4 (6.3%)
Myalgia	0 (0.0%)	4 (6.3%)
Muscular weakness	0 (0.0%)	3 (4.8%)
Muscle spasms	0 (0.0%)	3 (4.8%)
Neck pain	1 (3.1%)	2 (3.2%)
Tendonitis	0 (0.0%)	2 (3.2%)
Spinal pain	0 (0.0%)	2 (3.2%)
Arthritis	0 (0.0%)	1 (1.6%)
Bone pain	0 (0.0%)	1 (1.6%)
Osteoporosis	0 (0.0%)	1 (1.6%)
Rotator cuff syndrome	0 (0.0%)	1 (1.6%)
Joint swelling	0 (0.0%)	1 (1.6%)
Musculoskeletal discomfort	0 (0.0%)	1 (1.6%)
Synovial cyst	0 (0.0%)	1 (1.6%)
Trigger finger	0 (0.0%)	1 (1.6%)
Systemic lupus erythematosus	1 (3.1%)	0 (0.0%)
Subjects(filtered)	6 (18.8%)	31 (49.2%)
1stCollItemSubjects	32 (100.0%)	63 (100.0%)

Source: JRev309SelADSLSAFFL_Y AEDECODbyTRT01AfilTRTEMFL_Y PERIOD_RCP SOC_MUSCSK

Table 77: Adverse events by preferred terms, Blood and Lymphatic Disorders SOC, study 309

AEDECOD	PLACEBO	SA237
Neutropenia	1 (3.1%)	4 (6.3%)
Thrombocytopenia	1 (3.1%)	3 (4.8%)
Leukopenia	0 (0.0%)	2 (3.2%)
Anaemia	0 (0.0%)	2 (3.2%)
Hypofibrinogenaemia	0 (0.0%)	2 (3.2%)

AEDECOD	PLACEBO	SA237
Iron deficiency anaemia	0 (0.0%)	2 (3.2%)
Lymphopenia	0 (0.0%)	2 (3.2%)
Lymphadenopathy	0 (0.0%)	1 (1.6%)
Lymph node pain	0 (0.0%)	1 (1.6%)
Polycythaemia	0 (0.0%)	1 (1.6%)
Neutrophilia	0 (0.0%)	1 (1.6%)
Hyperfibrinogenaemia	1 (3.1%)	0 (0.0%)
Subjects(filtered)	3 (9.4%)	16 (25.4%)
1stCollItemSubjects	32 (100.0%)	63 (100.0%)

Source: JRevSelADSLSAFFL_Y AEDECODbyADSLTRT01AfilEPOCH_RCP SOC_BLOOD

Adverse event preferred terms occurring in 4 or more subjects in the satralizumab-mwge group are listed in [Table 78](#) for the ITT and in [Table 79](#) for anti-AQP4 IgG seropositive adults. Events that are more common in the group treated with satralizumab-mwge are shaded in both tables.

Reviewer Comment: There are no specific terms or groups of terms that raise a safety concern other than those noted above.

Table 78: Adverse events by preferred term, ITT, 4 or more subjects in SA 237 group, more than placebo shaded, study 309

AEDECOD	PLACEBO	SA237
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%)
Hypoaesthesia	0 (0.0%)	5 (7.9%)
Influenza	2 (6.3%)	5 (7.9%)
Insomnia	1 (3.1%)	5 (7.9%)
Diarrhoea	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%)
Oedema 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%)

AEDECOD	PLACEBO	SA237
Back pain	3 (9.4%)	4 (6.3%)
Fall	2 (6.3%)	4 (6.3%)
Subjects(filtered) with any AE	24 (75.0%)	58 (92.1%)
1stCollItemSubjects Total	32 (100.0%)	63 (100.0%)

Source: JRevSelADSLSAFFL_Y AEDECODbyADSLTRT01AfiltePOCH_RCP

Table 79: Adverse events by preferred term, anti-AQP4 IgG seropositive adults, 4 or more subjects in SA237 group, more than placebo shaded

AEDECOD	PLACEBO	SA237
Urinary tract infection	5 (21.7%)	8 (19.5%)
Rash	0 (0.0%)	7 (17.1%)
Arthralgia	0 (0.0%)	7 (17.1%)
Upper respiratory tract infection	5 (21.7%)	6 (14.6%)
Pain in extremity	2 (8.7%)	6 (14.6%)
Fatigue	1 (4.3%)	6 (14.6%)
Nausea	2 (8.7%)	6 (14.6%)
Pruritus	0 (0.0%)	5 (12.2%)
Nasopharyngitis	1 (4.3%)	5 (12.2%)
Depression	0 (0.0%)	4 (9.8%)
Cellulitis	0 (0.0%)	4 (9.8%)
Headache	3 (13.0%)	4 (9.8%)
Neutropenia	1 (4.3%)	4 (9.8%)
Blood creatine phosphokinase increased	1 (4.3%)	4 (9.8%)
Fall	1 (4.3%)	4 (9.8%)
Subjects(filtered)	16 (69.6%)	36 (87.8%)
1stCollItemSubjects	23 (100.0%)	41 (100.0%)

Source: JRevSelADSLSAFFL_Y AQP4J_POS AEDECODbyADSLTRT01AfiltePOCH_RCP

Injection-related reactions (IRR)

Injection-related reactions were indicated by a sponsor flag in the ADAE dataset. During the RCP there were 24 events in 8 subjects, 2 considered severe in the satralizumab-mwge group and 16 events in 5 subjects, all mild in the placebo group. The two severe events occurred in the same satralizumab-mwge subject ((b) (6)) on two separate occasions. In both cases the AE preferred term was vertigo.

Reviewer Comment: The vertigo for the above IRR was transient on both occasions and was not associated with any change in vital signs.

Table 80: Injection-related reaction sponsor flag, ITT, study 309

AEDECOD	PLACEBO	SA237
Diarrhoea	0 (0.0%)	2 (3.2%)
Urticaria	0 (0.0%)	1 (1.6%)
Swelling	0 (0.0%)	1 (1.6%)

AEDECOD	PLACEBO	SA237
Rash	0 (0.0%)	1 (1.6%)
Vertigo	0 (0.0%)	1 (1.6%)
Injection site pain	0 (0.0%)	1 (1.6%)
Diastolic hypotension	0 (0.0%)	1 (1.6%)
Erythema	0 (0.0%)	1 (1.6%)
Injection site bruising	0 (0.0%)	1 (1.6%)
Vision blurred	0 (0.0%)	1 (1.6%)
Micturition urgency	0 (0.0%)	1 (1.6%)
Nausea	0 (0.0%)	1 (1.6%)
Oedema	0 (0.0%)	1 (1.6%)
Pruritus	0 (0.0%)	1 (1.6%)
Feeling cold	1 (3.1%)	0 (0.0%)
Dizziness	1 (3.1%)	0 (0.0%)
Contusion	1 (3.1%)	0 (0.0%)
Burning sensation	1 (3.1%)	0 (0.0%)
Injection site erythema	2 (6.3%)	0 (0.0%)
Subjects(filtered)	5 (15.6%)	8 (12.7%)

Source: JRevSelADSLSAFFL_Y AEDECODbyADSLTRT01AfiltePOCH_RCP AEIRRFY_Y

Injection site reactions – ISR

Injection site reactions were indicated by a sponsor flag in the ADAE dataset. There were 14 such events in 5 placebo subjects, all mild. There were 14 such events in 8 satralizumab-mwge subjects, 12 mild and one moderate in severity.

Study 307

The most common adverse events by System Organ Class are listed for the full ITT in [Table 82](#) and for anti-AQP4 IgG seropositive adults in [Table 82](#). For the full ITT, 95.2% of the placebo group and 90.2% of the satralizumab-mwge group had at least one AE during the RCP. For anti-AQP4 IgG seropositive adults, all placebo subjects and 24 of 26 satralizumab-mwge subjects had at least one TEAE. The most common events for both treatment groups were infections.

Reviewer Comment: No single infection or type of infection was prominent in the satralizumab-mwge group. Events in the Blood and Lymphatic disorders are listed in [Table 83](#). Terms related to reductions in white blood cells are somewhat more prominent in the satralizumab-mwge group. The narrow SMQ for Haematopoietic leukopenia yields a proportion of 36.59% for the satralizumab-mwge group and 30.95% for the placebo group (MAED analysis). The odds ratio is 1.287 (0.469, 3.547; $p = 0.647$).

Table 81: Treatment-emergent adverse events by SOC, ITT, study 307

AEBODSYS	PLACEBO	SA237
Infections and infestations	26 (61.9%)	28 (68.3%)
Blood and lymphatic system disorders	9 (21.4%)	15 (36.6%)
Investigations	13 (31.0%)	15 (36.6%)
Gastrointestinal disorders	15 (35.7%)	14 (34.1%)
Musculoskeletal and connective tissue disorders	10 (23.8%)	14 (34.1%)
Nervous system disorders	10 (23.8%)	14 (34.1%)
Skin and subcutaneous tissue disorders	7 (16.7%)	14 (34.1%)
Injury, poisoning and procedural complications	6 (14.3%)	11 (26.8%)
General disorders and administration site conditions	9 (21.4%)	8 (19.5%)
Metabolism and nutrition disorders	9 (21.4%)	7 (17.1%)
Respiratory, thoracic and mediastinal disorders	4 (9.5%)	7 (17.1%)
Reproductive system and breast disorders	4 (9.5%)	6 (14.6%)
Vascular disorders	1 (2.4%)	6 (14.6%)
Eye disorders	3 (7.1%)	5 (12.2%)
Psychiatric disorders	2 (4.8%)	5 (12.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (7.1%)	3 (7.3%)
Cardiac disorders	1 (2.4%)	2 (4.9%)
Ear and labyrinth disorders	1 (2.4%)	2 (4.9%)
Endocrine disorders	1 (2.4%)	2 (4.9%)
Hepatobiliary disorders	3 (7.1%)	2 (4.9%)
Renal and urinary disorders	6 (14.3%)	2 (4.9%)
Congenital, familial and genetic disorders	0 (0.0%)	1 (2.4%)
Immune system disorders	1 (2.4%)	1 (2.4%)
Subjects(filtered) – with any TEAE	40 (95.2%)	37 (90.2%)
1stColItemSubjects – Total Subjects	42 (100.0%)	41 (100.0%)

Source: JRevSelADSLSAFFL_Y AESOCbyADSLTRT01AfiltEPOCH_RCP

Table 82: Treatment emergent adverse events by SOC, anti-AQP4 IgG seropositive adults, study 307

AEBODSYS	PLACEBO	SA237
Infections and infestations	17 (65.4%)	18 (69.2%)
Gastrointestinal disorders	12 (46.2%)	12 (46.2%)
Blood and lymphatic system disorders	6 (23.1%)	11 (42.3%)
Musculoskeletal and connective tissue disorders	6 (23.1%)	10 (38.5%)
Skin and subcutaneous tissue disorders	6 (23.1%)	10 (38.5%)
Investigations	9 (34.6%)	9 (34.6%)
Nervous system disorders	7 (26.9%)	8 (30.8%)
Injury, poisoning and procedural complications	4 (15.4%)	7 (26.9%)
Metabolism and nutrition disorders	7 (26.9%)	6 (23.1%)
Respiratory, thoracic and mediastinal disorders	4 (15.4%)	5 (19.2%)
Reproductive system and breast disorders	2 (7.7%)	5 (19.2%)
Eye disorders	2 (7.7%)	4 (15.4%)
Vascular disorders	1 (3.8%)	3 (11.5%)
Endocrine disorders	1 (3.8%)	2 (7.7%)
Ear and labyrinth disorders	1 (3.8%)	2 (7.7%)
Psychiatric disorders	1 (3.8%)	2 (7.7%)

AEBODSYS	PLACEBO	SA237
Renal and urinary disorders	1 (3.8%)	2 (7.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (7.7%)	2 (7.7%)
Cardiac disorders	1 (3.8%)	2 (7.7%)
General disorders and administration site conditions	8 (30.8%)	2 (7.7%)
Hepatobiliary disorders	3 (11.5%)	1 (3.8%)
Congenital, familial and genetic disorders	0 (0.0%)	1 (3.8%)
Immune system disorders	1 (3.8%)	1 (3.8%)
Subjects(filtered) with any TEAE	26 (100.0%)	24 (92.3%)
1stCollItemSubjects – Total Subjects	26 (100.0%)	26 (100.0%)

Source: JRevSelADSLSAFFL_Y AQP4J_POS AGEGR1_18 AESOCbyADSLTRT01AfiltePOCH_RCP

Table 83: Adverse events by preferred term, Blood and Lymphatic Disorders, ITT, study 307

AEDECOD	PLACEBO	SA237
Leukopenia	3 (7.1%)	6 (14.6%)
Lymphopenia	4 (9.5%)	3 (7.3%)
Anaemia	5 (11.9%)	3 (7.3%)
Iron deficiency anaemia	1 (2.4%)	2 (4.9%)
Neutropenia	2 (4.8%)	2 (4.9%)
Anaemia macrocytic	0 (0.0%)	1 (2.4%)
Pancytopenia	0 (0.0%)	1 (2.4%)
Hypofibrinogenaemia	0 (0.0%)	1 (2.4%)
Thrombocytopenia	1 (2.4%)	1 (2.4%)
Polycythaemia	0 (0.0%)	1 (2.4%)
Hypochromic anaemia	0 (0.0%)	1 (2.4%)
Hyperfibrinogenaemia	2 (4.8%)	0 (0.0%)
Leukocytosis	1 (2.4%)	0 (0.0%)
Autoimmune thrombocytopenia	1 (2.4%)	0 (0.0%)
Subjects(filtered)	9 (21.4%)	15 (36.6%)
1stCollItemSubjects	42 (100.0%)	41 (100.0%)

Source: JRevSelADSLSAFFL_Y AEDECODbyADSLTRT01AfiltePOCH_RCP SOC_BLOOD

Reviewer Comment: The events in Table 84 below

(b) (4)

(b) (4)

for Study 1.

Table 84: Treatment emergent adverse events by preferred term, ITT, 3 or more in SA237 and more than placebo shaded, study 307

AEDECOD	PLACEBO	SA237	Subjects(filtered)
Headache	4 (9.5%)	10 (24.4%)	14 (16.9%)
Upper respiratory tract infection	6 (14.3%)	10 (24.4%)	16 (19.3%)
Nasopharyngitis	7 (16.7%)	10 (24.4%)	17 (20.5%)
Urinary tract infection	7 (16.7%)	7 (17.1%)	14 (16.9%)
Leukopenia	3 (7.1%)	6 (14.6%)	9 (10.8%)
Hypercholesterolaemia	5 (11.9%)	4 (9.8%)	9 (10.8%)
Gastritis	0 (0.0%)	4 (9.8%)	4 (4.8%)
Back pain	5 (11.9%)	4 (9.8%)	9 (10.8%)

AEDECOD	PLACEBO	SA237	Subjects(filtered)
Arthralgia	0 (0.0%)	4 (9.8%)	4 (4.8%)
Pharyngitis	3 (7.1%)	4 (9.8%)	7 (8.4%)
Nausea	3 (7.1%)	3 (7.3%)	6 (7.2%)
Cystitis	4 (9.5%)	3 (7.3%)	7 (8.4%)
Urticaria	0 (0.0%)	3 (7.3%)	3 (3.6%)
Rhinitis	0 (0.0%)	3 (7.3%)	3 (3.6%)
Sinusitis	0 (0.0%)	3 (7.3%)	3 (3.6%)
Anaemia	5 (11.9%)	3 (7.3%)	8 (9.6%)
Oropharyngeal pain	1 (2.4%)	3 (7.3%)	4 (4.8%)
Lymphopenia	4 (9.5%)	3 (7.3%)	7 (8.4%)
Hypertension	0 (0.0%)	3 (7.3%)	3 (3.6%)
Subjects(filtered) – with any TEAE	40 (95.2%)	37 (90.2%)	83 (100.0%)
1stColItemSubjects – total subjects	42 (100.0%)	41 (100.0%)	(Denom=1stColTot)

Source: JRevSelADSLSAFFL_Y AEDECODbyADSLTRT01AfiltePOCH_RCP

Table 85: Treatment emergent adverse events by preferred term, anti-AQP4 IgG seropositive adults, 3 or more in SA237 and more than placebo shaded, study 307

AEDECOD	PLACEBO	SA237
Nasopharyngitis	4 (15.4%)	8 (30.8%)
Headache	3 (11.5%)	7 (26.9%)
Upper respiratory tract infection	3 (11.5%)	5 (19.2%)
Urinary tract infection	5 (19.2%)	4 (15.4%)
Gastritis	0 (0.0%)	4 (15.4%)
Leukopenia	3 (11.5%)	3 (11.5%)
Anaemia	3 (11.5%)	3 (11.5%)
Arthralgia	0 (0.0%)	3 (11.5%)
Pharyngitis	2 (7.7%)	3 (11.5%)
Back pain	4 (15.4%)	3 (11.5%)
Hypercholesterolaemia	5 (19.2%)	3 (11.5%)
Subjects(filtered)	26 (100.0%)	24 (92.3%)
1stColItemSubjects	26 (100.0%)	26 (100.0%)

Source: JRevSelADSLSAFFL_Y AQP4J_POS AGEGR1_18 AEDECODbyADSLTRT01AfiltePOCH_RCP

Injection-related reactions flag

The sponsor included a flag for adverse events related to administration of satralizumab-mwge and placebo. The number of events is relatively small but more common in the satralizumab-mwge group ([Table 86](#)). There were 40 individual events in 5 satralizumab-mwge subjects. One of these events in the satralizumab-mwge group was severe (Subject (b) (6)). There were 6 individual events in 2 placebo subjects, none severe.

Reviewer Comment: The IRR that was considered severe was an episode of elevated blood pressure to a maximum of 170/100 mm Hg at one hour after treatment from a baseline of 155/100. This was the 33rd injection of

satralizumab-mwge on day 896. The subject was treated with furosemide and the BP returned to normal within one hour. This subject had previous AEs of headache with many of the previous injections. There was no history of hypertension. The BP on day one was 145/90 mmHg.

Table 86: Injection-related adverse events flag, ITT, study 307

AEDECOD	PLACEBO	SA237
Headache	0 (0.0%)	2 (4.9%)
Rash	0 (0.0%)	1 (2.4%)
Pruritus	1 (2.4%)	1 (2.4%)
Pyrexia	1 (2.4%)	1 (2.4%)
Chills	0 (0.0%)	1 (2.4%)
Erythema	0 (0.0%)	1 (2.4%)
Face oedema	0 (0.0%)	1 (2.4%)
Flushing	0 (0.0%)	1 (2.4%)
Skin swelling	0 (0.0%)	1 (2.4%)
Hypertension	0 (0.0%)	1 (2.4%)
Injection site erythema	0 (0.0%)	1 (2.4%)
Local swelling	0 (0.0%)	1 (2.4%)
Oedema	0 (0.0%)	1 (2.4%)
Pain	0 (0.0%)	1 (2.4%)
Blood pressure decreased	1 (2.4%)	0 (0.0%)
Oedema mouth	1 (2.4%)	0 (0.0%)
Subjects(filtered)	2 (4.8%)	5 (12.2%)
1stCollItemSubjects	42 (100.0%)	41 (100.0%)

Source: JRevSelADSLSAFFL_Y AEDECODbyADSLTRT01AfitePOCH_RCP AEIRRFL_Y

Injection site Reactions

Twenty-one events considered injection site reactions occurred in 3 satralizumab-mwge subjects and in no placebo subject. None were severe or serious. Systemic symptoms occurred in 3 subjects and included flushing, a rash, and pruritis.

8.5.6 Laboratory Findings

Study 309

Hematology

- Neutrophils

The proportion of subjects with a neutrophil count below the lower limit of normal (LLN) at any time during the RCT was 28.1% in the placebo group and 33.3% in the satralizumab-mwge group. The proportion of subjects with a shift from normal to low was 25.0% in the placebo

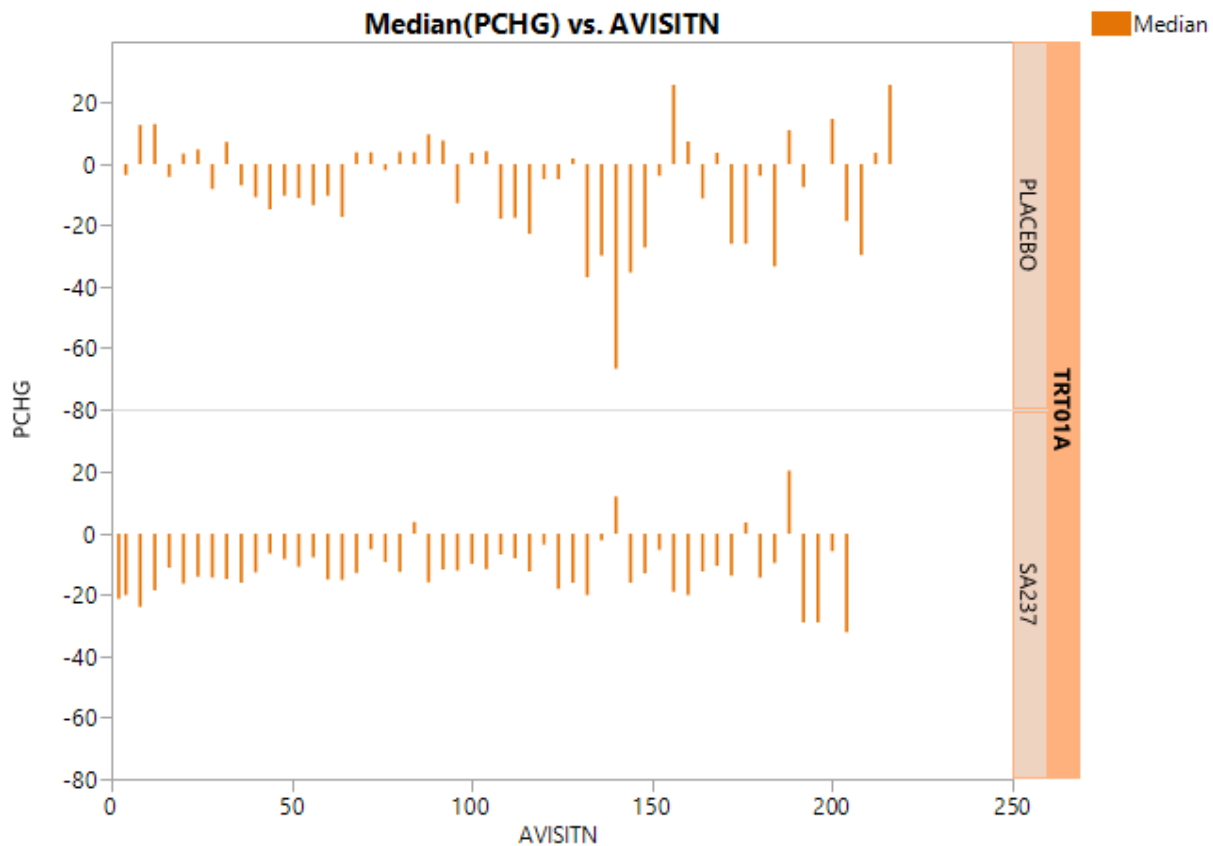
group and 30.2% in the satralizumab-mwge group. Two subjects in the satralizumab-mwge group had a neutrophil count below $0.5 \times 10^9/L$ during the RCP. The median percent reduction for all visits was 1% in the placebo group compared to 12% in the satralizumab-mwge group (Table 87). The small reduction was seen soon after the start of treatment and remained stable thereafter (Figure 6).

Table 87: Percent Change from baseline, all RCP visits, neutrophils, safety population, study 309

TRT01A	N Rows	Percent Change from Baseline				
		Mean	Std Dev	Min	Max	Median
PLACEBO	559	7.79	66.4	-79	644	-1
SA237	1591	-6.4	41	-91	275	-12

Source: LBTEST_NEUT Subset of EPOCH_RCP Subset of LB CAT_HEME Subset of ADLB 309 PCHG By (TRT01A).jmp

Figure 6: Median percent change from baseline, RCP, neutrophils, safety population, study 309



Source: Median PCHG RCP NEUT Study 309.jrp

Reviewer Comment: The modest reduction in neutrophil count is consistent with the Actemra label. The reduction was much more prominent in Study 307 (Figure 10), possibly because of the concurrent use of other immunosuppressants in that study.

- Lymphocytes

The proportion of subjects with a lymphocyte count below the LLN at any time was 25.0% of the placebo group and 38.1% for the satralizumab-mwge group. The proportion with a shift from normal to low was 15.6% in the placebo group compared to 23.8% in the satralizumab-mwge group. The median percent change was 15.4% in the placebo group and 0 in the satralizumab-mwge group.

Reviewer Comment: There is no consistent indication of a significant change in lymphocyte count with satralizumab-mwge treatment.

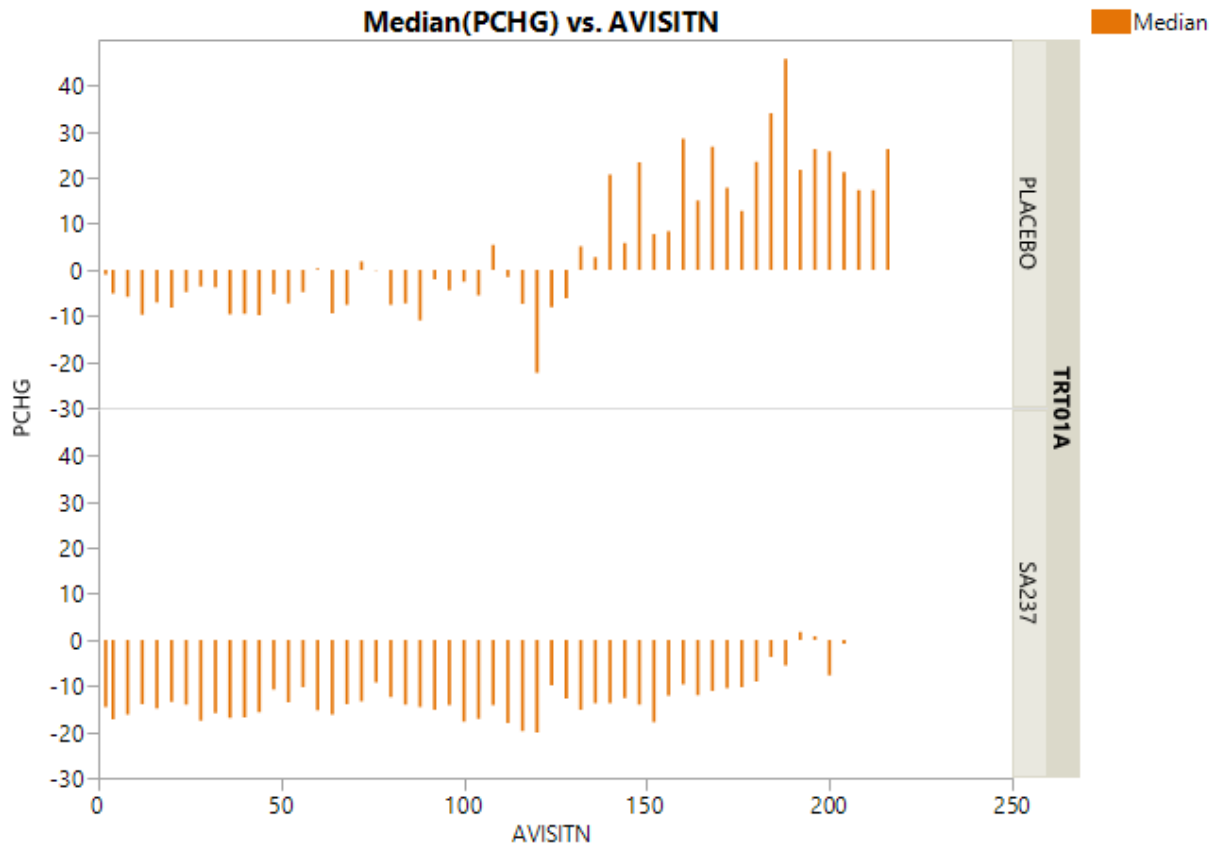
- Red blood cells, hemoglobin, hematocrit

There was no significant change in erythrocyte count, hemoglobin or hematocrit in either treatment group.

- Platelets

The proportion of subjects with a platelet count below the LLN was 12.5% in the placebo group compared to 25.4% in the satralizumab-mwge group. A shift from normal to low platelet count occurred in 3.1% of the placebo group compared to 20.6% of the satralizumab-mwge group. The median percent change from baseline for all visits was a decrease of 4.9% in the placebo group compared to a decrease of 14% in the satralizumab-mwge group. There were 9 instances of a platelet count below $100 \times 10^9/L$ in the placebo group and 28 events in 4 satralizumab-mwge subjects. There were no platelet counts below $50 \times 10^9/L$. The effect was seen soon after the start of treatment and remained stable thereafter. This is shown graphically by visit in Figure 7.

Figure 7: Median percent change from baseline, platelet count, safety population, study 309



Source: PCHGbyTRT01AbyAVISITN platelets study 309.jrp

Chemistry

- Liver transaminases, alkaline phosphatase, bilirubin, PT/INR

ALT

During the RCP, the proportion of subjects whose ALT shifted from the normal range to above ULN at any assessment was 12.5% in the placebo group compared to 36.5% in the satralizumab-mwge group ([Table 88](#)). A value above the ULN occurred in 12.5% of the placebo group compared to 38.1% of the satralizumab-mwge group. The median percent change from baseline was zero for the placebo group compared to an increase of 25 percent for the satralizumab-mwge group.

Table 88: Shift from baseline to RCP, ALT, safety population

SHIFT1	PLACEBO	SA237
(missing)	31 (96.9%)	63 (100.0%)
HIGH to NORMAL	0 (0.0%)	1 (1.6%)
NORMAL to HIGH	4 (12.5%)	23 (36.5%)
NORMAL to NORMAL	32 (100.0%)	62 (98.4%)
NORMAL to NULL	1 (3.1%)	5 (7.9%)
Subjects(filtered)	32 (100.0%)	63 (100.0%)
1stCollItemSubjects	32 (100.0%)	63 (100.0%)

Source: JRevSelADSLSAFFL_Y SHIFT1byADSLTRT01AfiltePOCH_RCP LBTEST_ALT

AST

During the RCP, the proportion of subjects whose AST shifted from the normal range to above ULN at any assessment was 6.3% in the placebo group compared to 20.6 % in the satralizumab-mwge group ([Table 89](#)). The proportion of subjects being treated with placebo who had at least one value above the ULN was 6.3% compared to 22.2% of the satralizumab-mwge group.

Table 89: Shift from baseline to RCP, AST, safety population

SHIFT1	PLACEBO	SA237
(missing)	31 (96.9%)	63 (100.0%)
HIGH to NORMAL	0 (0.0%)	1 (1.6%)
NORMAL to HIGH	2 (6.3%)	13 (20.6%)
NORMAL to NORMAL	32 (100.0%)	62 (98.4%)
NORMAL to NULL	4 (12.5%)	9 (14.3%)
Subjects(filtered)	32 (100.0%)	63 (100.0%)
1stCollItemSubjects	32 (100.0%)	63 (100.0%)

Source: JRevSelADSLSAFFL_Y SHIFT1byADSLTRT01AfiltePOCH_RCP LBTEST_AST

Bilirubin

During the RCP, the proportion of subjects whose bilirubin changed from the normal range to above ULN at any assessment was 36.5% compared to 12.5% in the placebo group ([Table 90](#)). There were no placebo subjects with a bilirubin level above ULN whereas 12.7% of subjects treated with satralizumab-mwge had a level above ULN. The median increase was 0 in the placebo group compared to 29.3% in the satralizumab-mwge group.

Table 90: Shift from baseline to RCP, bilirubin, safety population

SHIFT1	PLACEBO	SA237
(missing)	31 (96.9%)	63 (100.0%)
LOW to LOW	6 (18.8%)	11 (17.5%)
LOW to NORMAL	6 (18.8%)	10 (15.9%)
NORMAL to HIGH	0 (0.0%)	8 (12.7%)
NORMAL to LOW	13 (40.6%)	13 (20.6%)

SHIFT1	PLACEBO	SA237
NORMAL to NORMAL	26 (81.3%)	51 (81.0%)
NORMAL to NULL	1 (3.1%)	5 (7.9%)
Subjects(filtered)	32 (100.0%)	63 (100.0%)
1stCollItemSubjects	32 (100.0%)	63 (100.0%)

Source: JRevSelADSLSAFFL_Y SHIFT1byADSLTRT01AfiltePOCH_RCP LBTEST_BILI

ALP

There was no difference between the treatment groups in the proportion with a shift in ALP from normal to high.

Hy's Law

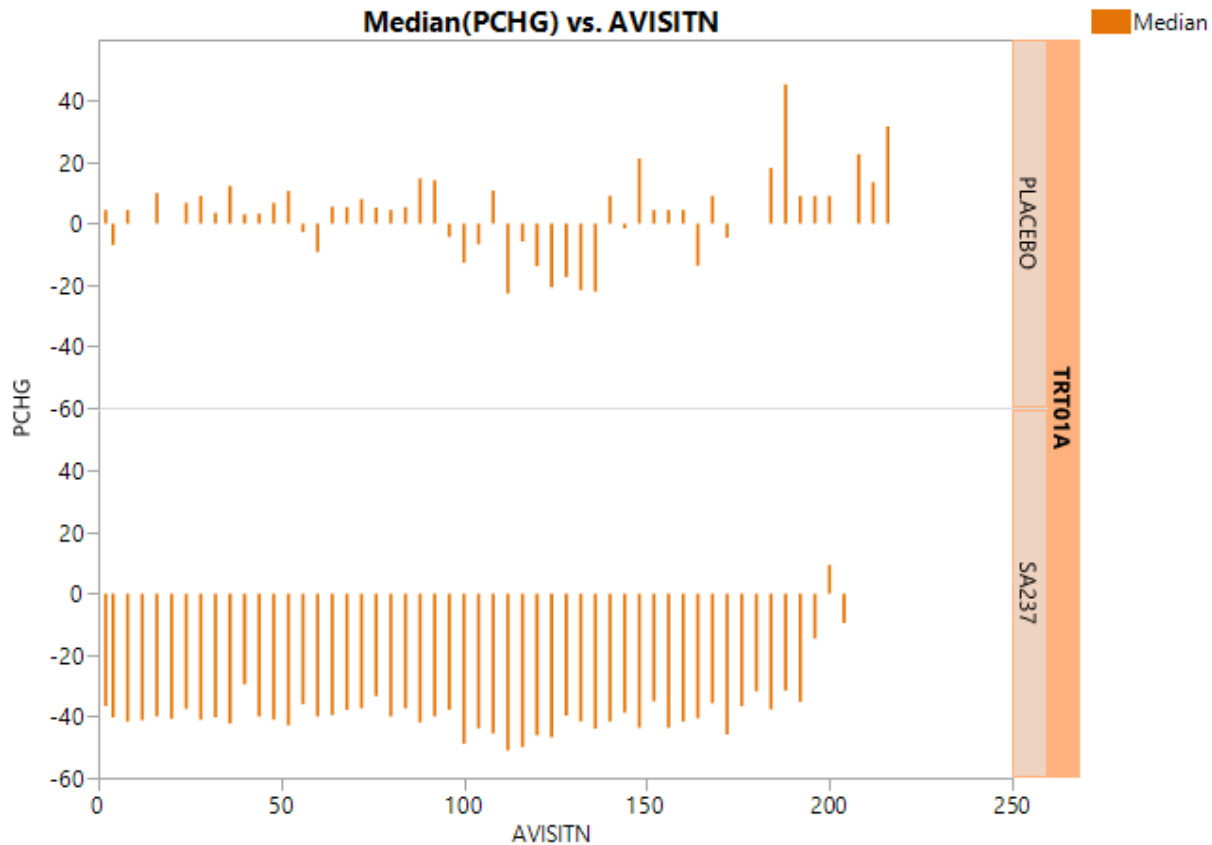
There were no subjects in either treatment group that met the criteria for Hy's Law at any assessment in the RCP or OLE. Two subjects, both treated with satralizumab-mwge did have an elevation of ALT and AST between 2- and 5-times the ULN but the bilirubin remained normal and, in both cases, the elevation was transient.

- Fibrinogen

The proportion of subjects with a fibrinogen level below the LLN at one or more assessments was 25.0% for the placebo group and 77.8% for the satralizumab-mwge group. For all assessments, the median percent reduction in fibrinogen levels was -40% in the group treated with satralizumab-mwge compared to an increase of 4.35% for the placebo group. The reduction in the satralizumab-mwge group was seen from the beginning of treatment during the RCP (**Figure 8**). The percent change for the subjects treated with the placebo during the RCP and who entered the OLE was -32%, which is comparable to the satralizumab-mwge group during the same period (-37%).

Reviewer Comment: Interactions with the sponsor in February 2018, involved a concern that the sponsor may have introduced bias by assuming that fibrinogen levels could be used to identify subjects by treatment assignment and that this could be used as a guide to the need for a sample size reassessment. Based on the trial results, it appears that this assumption could have partially unblinded those involved in that analysis.

Figure 8: Fibrinogen, median change from baseline, RCP, study 309



Source: Median PCHG Fibrinogen byAVISITNbyTRT01A during RCP study 309.jrp

- Prothrombin time/International Normalized ratio

During the RCP, 31.3% of placebo subjects had an INR above the upper limit of normal (ULN) compared to 46.0% of subjects treated with satralizumab-mwge. A shift from baseline normal to above the ULN was seen in 39.7% of subjects treated with satralizumab-mwge compared to 21.9% of subjects treated with placebo. The median change was 0% for both treatment groups.

Reviewer Comment: Along with the changes in bilirubin (Table 90), there is a suggestion of a small change in liver function in patients treated with satralizumab-mwge. Hepatotoxicity is included in the Warnings and Precautions section of the Actemra label and monitoring for liver function studies is recommended

(https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125276s127,125472s0401bl.pdf).

- LDL Cholesterol and Triglycerides

During the RCP the proportion of subjects with a shift from normal to high LDL cholesterol was higher in the subjects being treated with satralizumab-mwge (41.3%) compared to those being treated with placebo (25.0%). A similar difference was seen for triglycerides, 36.5% compared to 28.1%. The median percent change was a reduction of 11% in the placebo group compared to a 6% increase in the satralizumab-mwge group.

Reviewer Comment: The Actemra label does include a Warning for elevations of various lipid parameters based on the results of controlled clinical trials in patients with Rheumatoid Arthritis.

- Creatinine, Urea nitrogen

There were no significant effects on serum creatinine or on blood urea nitrogen

- Lactic dehydrogenase

A slightly higher proportion of subjects being treated with satralizumab-mwge had a shift from normal to high LDH levels, 22.2% compared to the placebo group, 12.5%.

- Complement levels

There appears to be a significant reduction in C3 ([Table 91](#)) and C4 components ([Table 92](#)) of the complement system. There is a reduction in CH50 activity as well ([Table 93](#)). The reduction is seen at the onset of treatment and appears to be stable thereafter ([Figure 9](#)).

Table 91: Percent change from baseline, C3 complement, RCP, safety population, study 309

TRT01A	N	Percent change from baseline				
		Mean	Std Dev	Min	Max	Median
PLACEBO	524	3.56	16.5	-41	66.7	0
SA237	1516	-22	14.4	-63	60	-25

Source: LBTEST_C3 Subset of Not missing BL DISC Subset of EPOCH_RCP Subset of LBCAT_COMPL Subset of ADLB 309 PCHG By (TRT01A).jmp

Table 92: Percent change from baseline, C4 complement, RCP, safety population, study 309

TRT01A	N	Percent change from baseline				
		Mean	Std Dev	Min	Max	Median
PLACEBO	524	1.82	22.6	-89	130	0
SA237	1516	-44	21.6	-93	48.4	-50

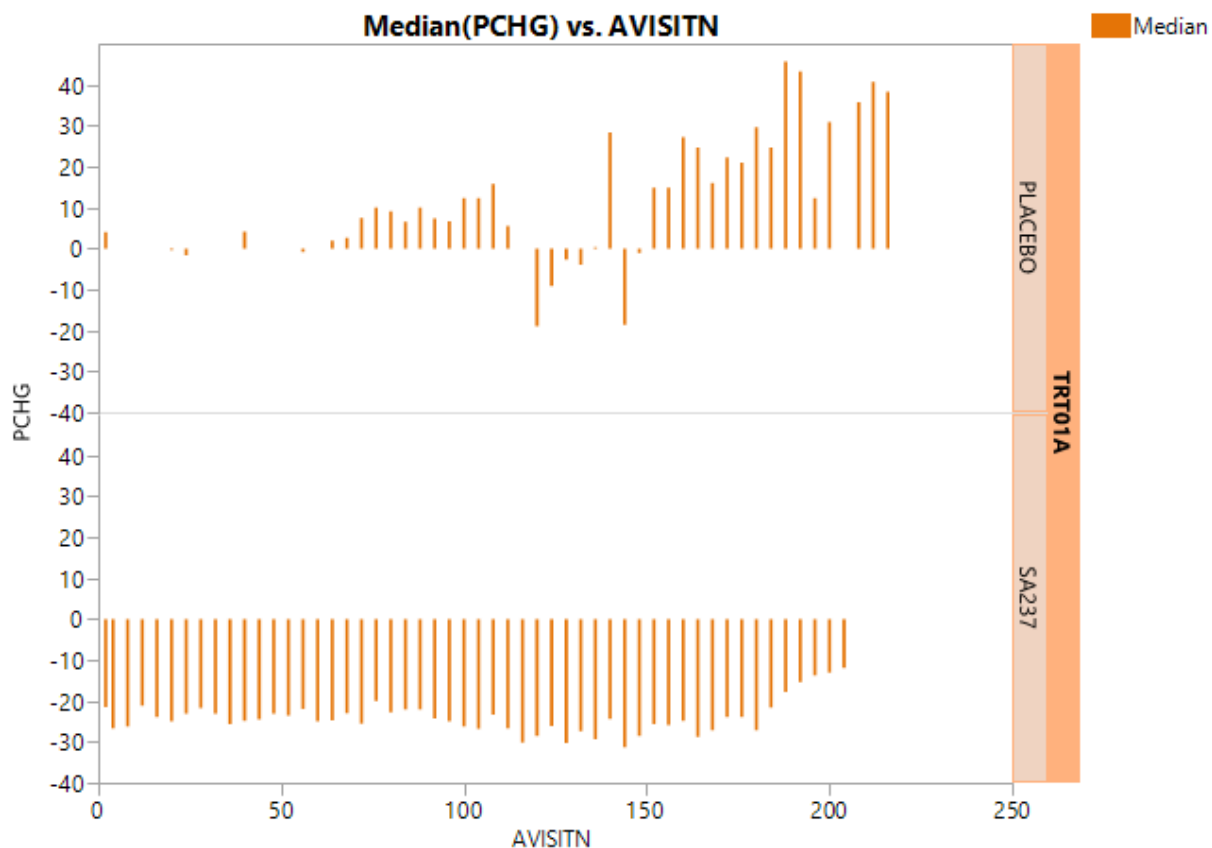
Source: LBTEST_C4 Subset of Not missing BL DISC Subset of EPOCH_RCP Subset of LBCAT_COMPL Subset of ADLB 309 PCHG By (TRT01A).jmp

Table 93: Percent change from baseline, CH50, RCP, safety population, study 309

TRT01A	N	Percent change from baseline				
		Mean	Std Dev	Min	Max	Median
PLACEBO	527	19.4	61.6	-61	376	2.73
SA237	1511	-30	28.2	-81	121	-35

Source: LBTEST_CH50 Subset of Not missing BL DISC Subset of EPOCH_RCP Subset of LBCAT_COMPL Subset of ADLB 309 PCHG By (TRT01A).jmp

Figure 9: Percent change from baseline by visit, C3 complement, RCP, safety population, study 309



Source: PCHG C3byAVISITN RCP Study 309.jrp

Study 307

Hematology

- Neutrophils

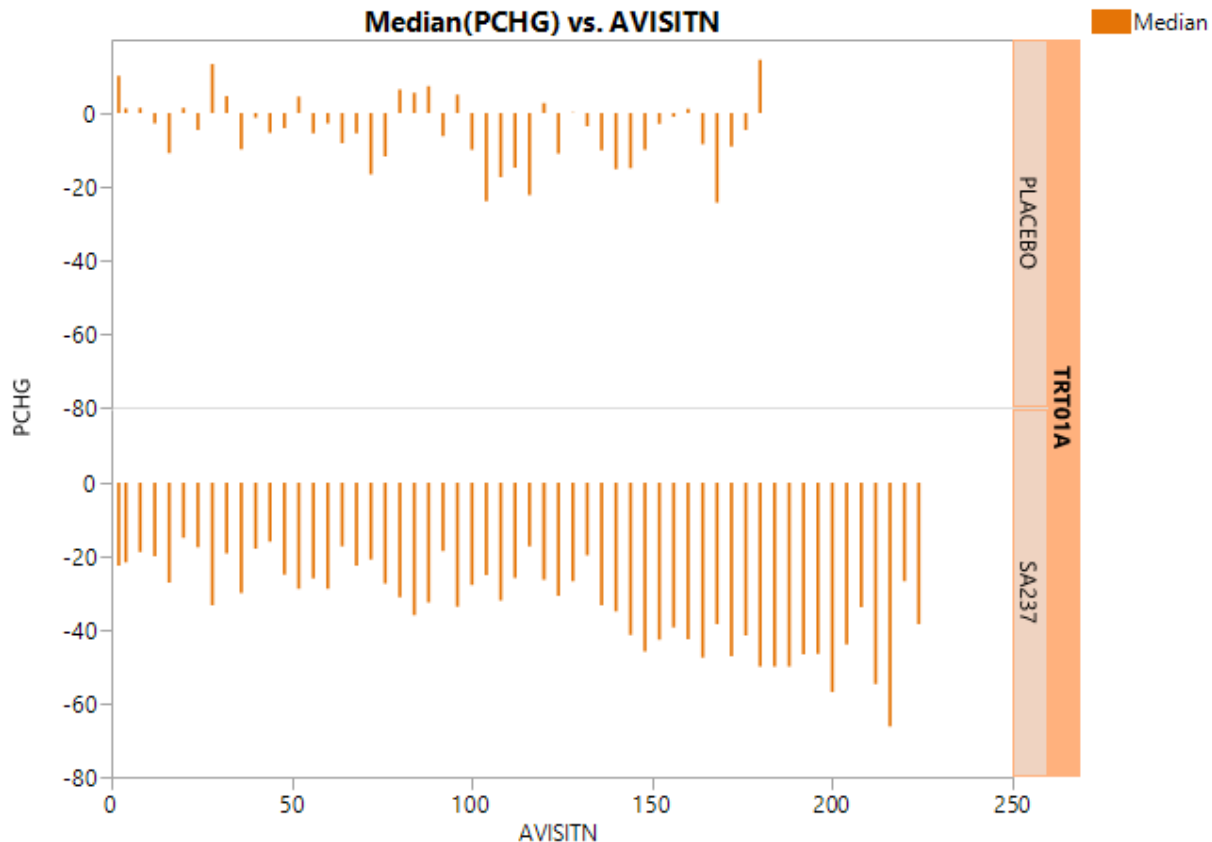
The proportion of subjects with a neutrophil count below the lower limit of normal (LLN) at any time during the RCT was 21.4% in the placebo group and 29.3% on the satralizumab-mwge group. The proportion of subjects with a shift from normal to low was 19.0% in the placebo group and 29.3% in the satralizumab-mwge group. No subject in the satralizumab-mwge group had a neutrophil count below $0.5 \times 10^9/L$ during the RCP. However, the percent change from baseline for all visits during the RCT shows that there were reduced neutrophil counts in the satralizumab-mwge group ([Table 94](#)). This is more evident when depicted by visit in [Figure 10](#).

Table 94: Percent change from baseline during the RCP, neutrophil count, Study 307

TRT01A	N	Percent change from baseline				
		Mean	Std Dev	Min	Max	Median
PLACEBO	833	7.01	47.5	-78	292	-2.7
SA237	1080	-19	37.8	-86	252	-27

Source: LBTEST_NEUT Subset of EPOCH_RCP Subset of LBCAT_HEME Subset of ADLB 307 PCHG By (TRT01A).jmp

Figure 10: Neutrophil count by visit during the RCP, safety population, Study 307



Source: Median PCHG NEUT RCP Study 307.jpg

- Lymphocytes

The proportion of subjects with a lymphocyte count below the LLN at any time was 66.7% of the placebo group and 70.7% for the satralizumab-mwge group. The proportion with a shift from normal to low was 26.2% in the placebo group compared to 51.2% in the satralizumab-mwge group. The median percent change in lymphocyte count during the RCP was an increase of 15.4% in the placebo group compared to a 0% median change in the satralizumab-mwge group.

Reviewer Comment: *There is no consistent change in lymphocyte count with satralizumab-mwge treatment. This is similar to the result in Study 309.*

- Red blood cells, hemoglobin, hematocrit

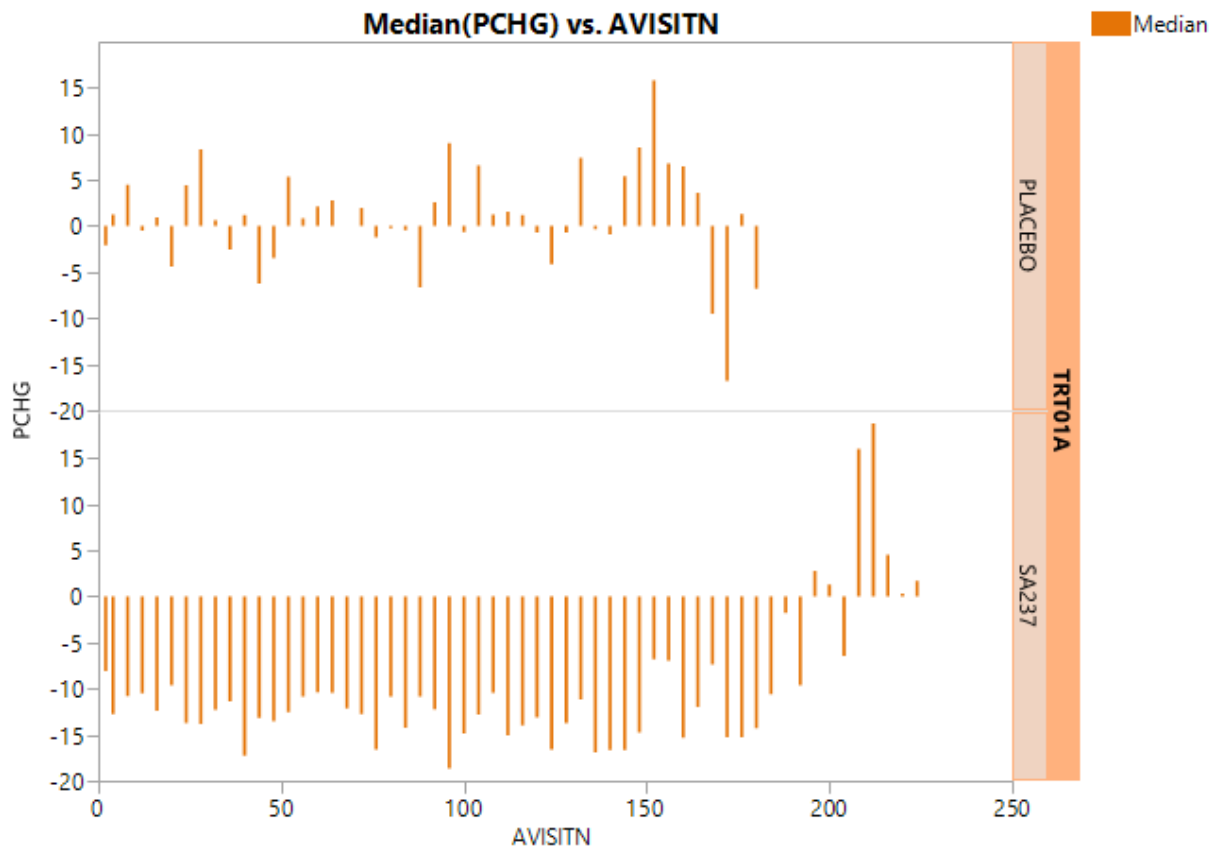
There was no significant change in Erythrocyte count, hemoglobin or hematocrit in either

treatment group.

- Platelets

The proportion of subjects with a platelet count below the LLN ($150 \times 10^9/L$) was 21.4% in the placebo group compared to 29.3% in the satralizumab-mwge group. A shift from normal to low platelet count occurred in 14.3% of the placebo group compared to 26.8% of the satralizumab-mwge group. The median change over all visits was an increase of 1.2% in the placebo group compared to a decrease of 13% in the satralizumab-mwge group. During the RCP there were no subjects with a platelet count below $100 \times 10^9/L$. The effect was seen soon after the start of treatment and remained stable thereafter. This is shown graphically by visit in [Figure 11](#).

Figure 11: Median percent change from baseline, platelet count, RCP, study 307



Source: Median PCHG PLATELETS RCP Study 307.jrp

Chemistry

- Liver transaminases, alkaline phosphatase, bilirubin, PT/INR

ALT

During the RCP, the proportion of subjects whose ALT shifted from the normal range at baseline to above ULN at any assessment was 11.9% in the placebo group compared to 12.2% in the satralizumab-mwge group. A value that was above the ULN at any assessment occurred in 14.3% of the placebo group compared to 19.5% in the satralizumab-mwge group. The median change from baseline over all assessments was zero for both treatment groups.

Reviewer Comment: There is no indication of an elevation of ALT in Study 307. There was a potentially significant increase in ALT in Study 309 (Table 88).

AST

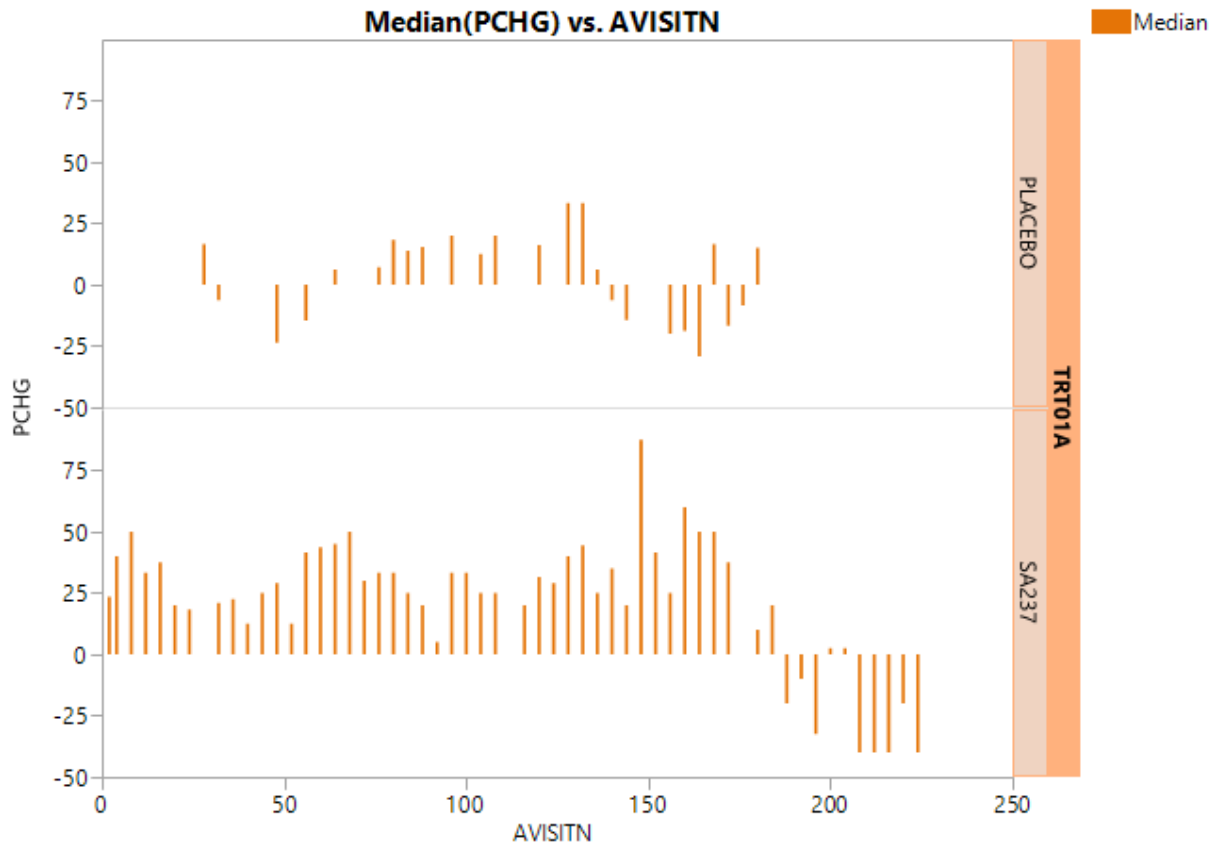
During the RCP, the proportion of subjects whose AST shifted from the normal range to above ULN at any assessment was 19.0% in the placebo group compared to 14.6 % in the satralizumab-mwge group. The proportion with a value above the ULN at any assessment was 19.0% for the placebo group and 17.1% for the satralizumab-mwge group. The median percent change was zero in the placebo group and an increase of less than 1% in the satralizumab-mwge group.

Reviewer Comment: Unlike in Study 309 (Table 89), there is no indication of an elevation of AST in Study 307.

Bilirubin

No subjects being treated with placebo with a normal bilirubin prior to treatment shifted to a level above the ULN during treatment; 4 subjects treated with satralizumab-mwge shifted from normal at baseline to above normal during treatment. No subjects treated with placebo had a bilirubin level above ULN during the RCP whereas there were 4 such satralizumab-mwge subjects. The median change from baseline was zero for the placebo group but an increase of 25% in the satralizumab-mwge group. This is more evident when displayed over time

Figure 12: Median percent change from baseline, RCP, bilirubin, safety population, study 307



Source: Median PCHG RCP BILI Study 307.jrp

Alkaline phosphatase

There was no significant difference between placebo and satralizumab-mwge in the proportion of subjects with a change from baseline in alkaline phosphatase.

Hy's Law

There were no subjects in either treatment group who met the criteria for Hy's Law at any assessment in the RCP or OLE. Two subjects, both treated with satralizumab-mwge did have an elevation of ALT and AST between 2- and 5-times the ULN but the bilirubin remained normal.

Reviewer Comment:

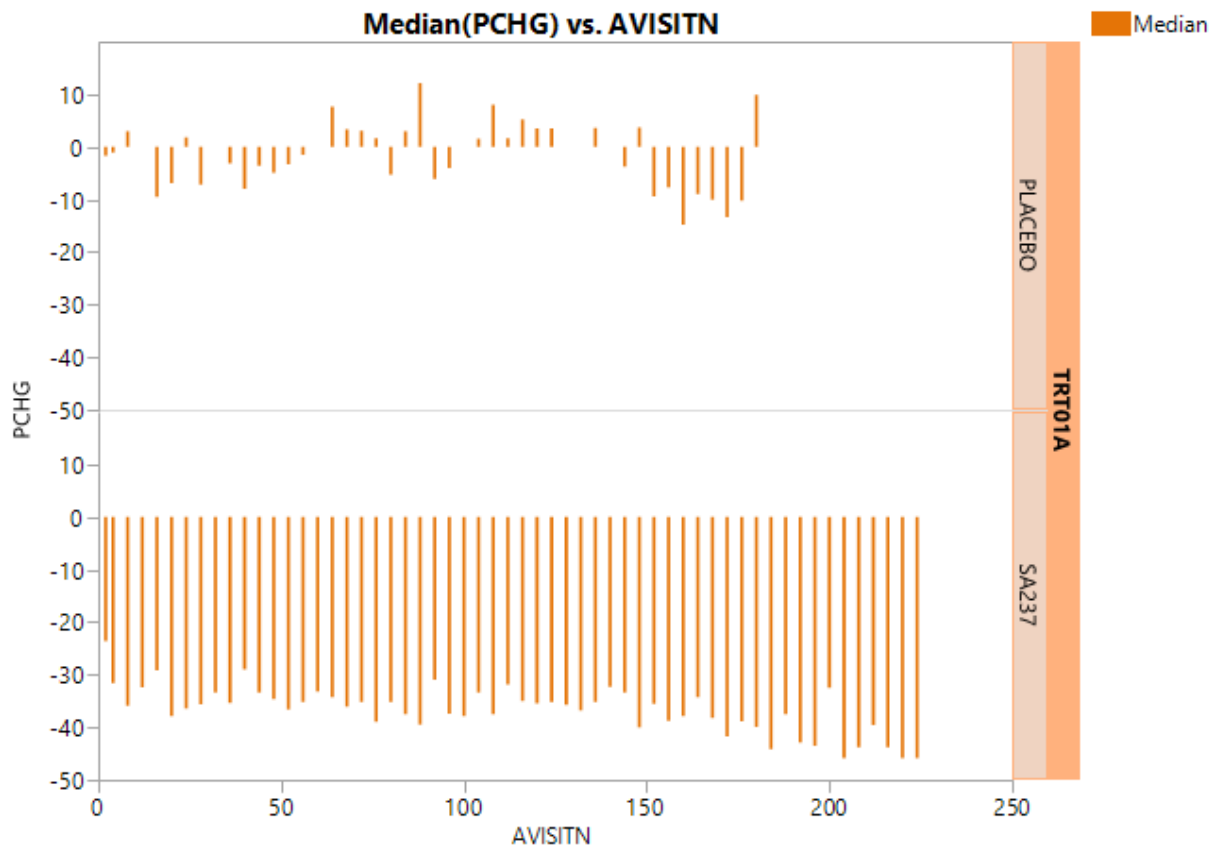
One subject ((b) (6)), a 31-year old Asian female, had an elevation of liver transaminases more than 5 times ULN with no change in bilirubin or ALP. The only relevant concurrent medication at baseline were azathioprine, 50 mg b.i.d. and prednisolone t.i.d. She was randomized to satralizumab-mwge and had received the initial 3 loading doses by day 29. On Study Day 13, she had a non-serious adverse event (AE) of moderate bronchitis. She received treatment with amoxicillin, clavulanic acid, and budesonide for the event. The transaminase elevations were noted on day 15 but became above 5X normal on day 29, the day of the third dose. Satralizumab-mwge was withdrawn and the elevations resolved by day 106. The event is confounded by the use amoxicillin/clavulanate which has a label warning for liver toxicity.

Subject (b) (6) was a 14-year old Black or African-American female. At initial screening ANA and anti-DNA antibody were above normal. Baseline medications included mycophenolate and low dose prednisone. She was randomized to placebo and had no adverse events during the RCP. The last dose of placebo was on study day 233. She enrolled in the OLE and received the first dose of satralizumab-mwge on study day 304. She had received a total of 7 doses of satralizumab-mwge by day 442. An SAE of SLE was reported on day 442. An episode of optic neuritis occurred on day 472 which was treated with corticosteroids. Vision returned to normal. She was hospitalized on day 517 with clinical and laboratory manifestations of systemic inflammation. She also developed sepsis attributed to an infected central venous catheter. A transient elevation of liver transaminases occurred beginning on day 516 and resolved by day 522.

- Fibrinogen

The proportion of subjects with a shift from normal at baseline to low at any assessment during the RCP was 19.0% for the placebo group compared to 48.8% for the satralizumab-mwge group. The proportion of subjects with a fibrinogen level below the LLN at any visit was 21.4% for the placebo group and 65.9% for the satralizumab-mwge group. For all assessments during the RCP, the median percent change in fibrinogen levels was 0% for the placebo group compared to -35% in the group treated with satralizumab-mwge. The reduction in the satralizumab-mwge group was seen from the beginning of treatment during the RCP ([Figure 13](#)). The percent change for the subjects treated with the placebo during the RCP and who entered the OLE was -34%, which is comparable to the satralizumab-mwge group during the same period (-35%).

Figure 13: Median percent change from baseline, fibrinogen, RCP, safety population, Study 307



Source: Median PCHG FIBRINO RCP Study 307.jrp

- Prothrombin time/International Normalized ratio

During the RCP, 16.7% of placebo subjects had an INR above the upper limit of normal (ULN) compared to 26.8 of subjects treated with satralizumab-mwge. A shift from baseline normal to above the ULN was seen in 14.3% of subjects treated with satralizumab-mwge compared to 22.0% of subjects treated with placebo. The median percent change was 0% for both groups.

Reviewer Comment: The changes in PT/INR and bilirubin seen in study 309 were not seen in study 307.

- LDL Cholesterol and Triglycerides

During the RCP the proportion of subjects with a shift from normal to high LDL cholesterol was approximately the same in those being treated with satralizumab-mwge (31.7%%) compared to

those being treated with placebo (33.3%). A shift from normal to high triglyceride level was seen in 26.2% of the placebo group compared to 41.5% of the satralizumab-mwge group.

- Creatinine, Urea nitrogen

There were no significant effects on serum creatinine or on blood urea nitrogen

- Lactic dehydrogenase

There was no difference in the proportion of subjects with a change in LDH levels

- Complement

There was a reduction in the level of C3 ([Table 95](#)) and C4 ([Table 96](#)) components of complement as well as in the CH50 assay ([Table 97](#)). The reduction was seen soon after the start of treatment and remained stable thereafter ([Figure 14](#)).

Table 95: C3 complement, RCP, safety population, Study 307

TRT01A	N	Percent change from baseline				
		Mean	Std Dev	Min	Max	Median
PLACEBO	808	-0	12.3	-38	60	0
SA237	1063	-18	11.7	-46	36.4	-20

Source: LBTEST_C3 Subset of EPOCH_RCP Subset of LBCAT_COMPL Subset of ADLB 307 PCHG By (TRT01A).jmp

Table 96: C4 complement, RCP, safety population, Study 307

TRT01A	N	Percent change from baseline				
		Mean	Std Dev	Min	Max	Median
PLACEBO	808	0.55	16.5	-47	84.4	-1
SA237	1063	-47	15.9	-76	30.7	-51

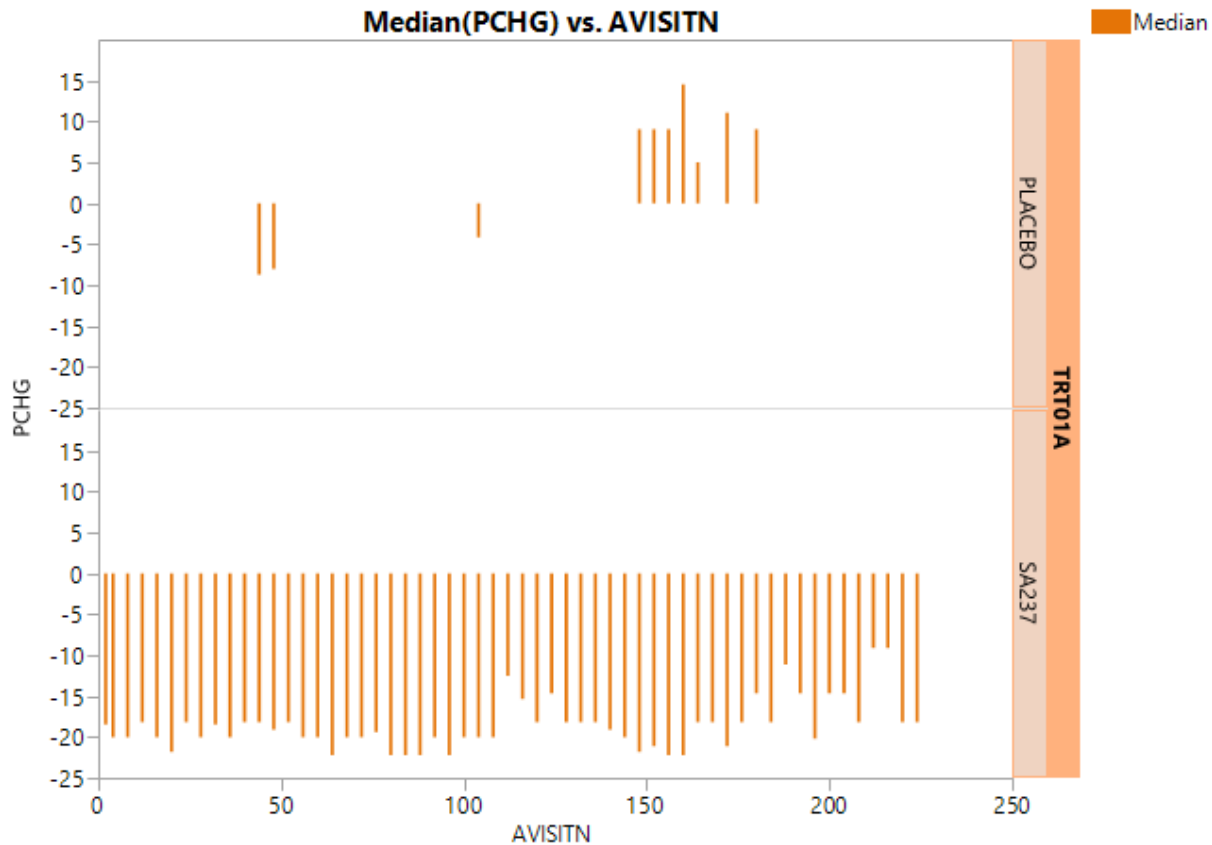
Source: LBTEST_C4 Subset of EPOCH_RCP Subset of LBCAT_COMPL Subset of ADLB 307 PCHG By (TRT01A).jmp

Table 97: CH50, RCP, safety population, Study 307

TRT01A	N	Percent change from baseline				
		Mean	Std Dev	Min	Max	Median
PLACEBO	804	-2.4	38.3	-76	275	-9.5
SA237	1068	-38	20.9	-83	61.3	-41

Source: LBTEST_CH50 Subset of EPOCH_RCP Subset of LBCAT_COMPL Subset of ADLB 307 PCHG By (TRT01A).jmp

Figure 14: C3 complement, RCP, safety population, Study 307



Source: Median PCHG C3 RCP study 307.jrp

8.5.7 Vital Signs

Study 309

There were no significant changes in systolic or diastolic blood pressure (DBP) over the 60 minutes after injections in either treatment group. However, there was an increased proportion of subjects treated with satralizumab-mwge who had an elevated systolic blood pressure (SBP) of 140 to 160 mm Hg at the any assessment, and a smaller increase in the proportion with an SBP over 160 mm Hg ([Table 98](#)). There were no significant changes in DBP ([Table 99](#)). A pulse rate of less than 60 was seen more frequently in the satralizumab-mwge group ([Table 100](#)).

Table 98: Systolic blood pressure, RCP, study 309

AVALCAT	VSTPT	PLACEBO	SA237
<90 mmHg	Pre-Dose	4 (12.5%)	3 (4.8%)
	15 Minutes Post-Dose	4 (12.5%)	6 (9.5%)

AVALCAT	VSTPT	PLACEBO	SA237
	60 Minutes Post-Dose	2 (6.3%)	2 (3.2%)
	(missing)	0 (0.0%)	1 (1.6%)
	Pre-Dose	6 (18.8%)	25 (39.7%)
>140-160 mmHg	15 Minutes Post-Dose	6 (18.8%)	27 (42.9%)
	60 Minutes Post-Dose	6 (18.8%)	24 (38.1%)
	Pre-Dose	0 (0.0%)	8 (12.7%)
>160 mmHg	15 Minutes Post-Dose	0 (0.0%)	8 (12.7%)
	60 Minutes Post-Dose	1 (3.1%)	8 (12.7%)
	Subjects(filtered)	32 (100.0%)	63 (100.0%)
	1stCollItemSubjects	32 (100.0%)	63 (100.0%)

JRevSelADSL309SAFFL_Y AVALCATbyVSTPTbyTRT01AfiltEPOCH_RCP ANL01FL_Y PARAM_SBP

Table 99: Diastolic blood pressure, RCP, study 309

AVALCAT	VSTPT	PLACEBO	SA237
	Pre-Dose	1 (3.1%)	2 (3.2%)
<50 mmHg	15 Minutes Post-Dose	1 (3.1%)	3 (4.8%)
	60 Minutes Post-Dose	1 (3.1%)	1 (1.6%)
	Pre-Dose	0 (0.0%)	4 (6.3%)
>100 mmHg	15 Minutes Post-Dose	1 (3.1%)	5 (7.9%)
	60 Minutes Post-Dose	0 (0.0%)	2 (3.2%)
	(missing)	0 (0.0%)	1 (1.6%)
	Pre-Dose	7 (21.9%)	17 (27.0%)
>90-100 mmHg	15 Minutes Post-Dose	13 (40.6%)	18 (28.6%)
	60 Minutes Post-Dose	8 (25.0%)	21 (33.3%)
	Subjects(filtered)	32 (100.0%)	63 (100.0%)
	1stCollItemSubjects	32 (100.0%)	63 (100.0%)

JRevSelADSL309SAFFL_Y AVALCATbyVSTPTbyTRT01AfiltEPOCH_RCP ANL01FL_Y PARAM_DBP

Table 100: Pulse rate, RCP, study 309

AVALCAT	VSTPT	PLACEBO	SA237
<60 beats/min	(missing)	1 (3.1%)	0 (0.0%)
	Pre-Dose	8 (25.0%)	23 (36.5%)
	15 Minutes Post-Dose	7 (21.9%)	28 (44.4%)
	60 Minutes Post-Dose	8 (25.0%)	26 (41.3%)
>100 beats/min	Pre-Dose	3 (9.4%)	8 (12.7%)
	15 Minutes Post-Dose	2 (6.3%)	6 (9.5%)
	60 Minutes Post-Dose	1 (3.1%)	6 (9.5%)
	Subjects(filtered)	32 (100.0%)	63 (100.0%)
	1stCollItemSubjects	32 (100.0%)	63 (100.0%)

Source: JRevSelADSL309SAFFL_Y AVALCATbyVSTPTbyTRT01AfiltEPOCH_RCP ANL01FL_YPARAM_PR

Study 307

There were no significant changes in blood pressure or pulse rate in study 307.

8.5.8 Electrocardiograms (ECGs)

In study 309 there was a general interpretation of an ECG as “abnormal” one or more times during the RCP in 41% of placebo subjects and 54% of satralizumab-mwge subjects. In study 307, 22% of the placebo group and 41% of the satralizumab-mwge group had one or more ECGs interpreted as abnormal.

Reviewer Comment: These abnormalities were most commonly abnormal intervals, abnormalities of T- or U-wave morphology that were not associated with symptoms. Although adverse events in the Cardiac SOC were slightly more common in the satralizumab-mwge group, the preferred terms did not suggest a specific safety concern.

8.5.9 QT

Study 309

QTcF prolongation was slightly more common in subjects treated with satralizumab-mwge ([Table 101](#)). Five subjects had a prolongation of more than 60 msec compared to one subject treated with placebo ([Table 102](#)). There were 5 subjects with an AE in the Cardiac SOC, all treated with satralizumab-mwge. Two of the events were serious, one of bradycardia and one of Lateral ST Elevation myocardial infarction.

Table 101: QTcF by category, RCP, study 309

AVALCAT	PLACEBO	SA237
<=450ms	30 (93.8%)	62 (98.4%)
>450 to <=480ms	5 (15.6%)	13 (20.6%)
>480 to <=500ms	1 (3.1%)	3 (4.8%)
>500ms	1 (3.1%)	3 (4.8%)
Subjects(filtered)	32 (100.0%)	63 (100.0%)
1stCollItemSubjects	32 (100.0%)	63 (100.0%)

Source: JRevSelADSL309SAFFL_Y AVALCATbyTRT01PfiltPARAM_QTcF APERIODC_RCP

Table 102: QTcF, change from baseline, RCP, study 309

CHGCAT	PLACEBO	SA237
(missing)	31 (96.9%)	62 (98.4%)
>0 to <=30ms	13 (40.6%)	50 (79.4%)
>30 to <=60ms	1 (3.1%)	12 (19.0%)
>60ms	1 (3.1%)	5 (7.9%)
Subjects(filtered)	32 (100.0%)	63 (100.0%)
1stCollItemSubjects	32 (100.0%)	63 (100.0%)

Source: JRevSelADSL309SAFFL_Y CHGCATbyTRT01AfiltPARAM_QTcF APERIODC_RCP

Study 307

There were no significant differences between the treatment groups for changes in the QTcF in study 307 (Table 103 and Table 104). There were 2 AEs of bradycardia, neither considered serious.

Table 103: QTcF by category, RCP, study 307

AVALCAT	PLACEBO	SA237
<=450ms	40 (95.2%)	41 (100.0%)
>450 to <=480ms	4 (9.5%)	8 (19.5%)
>480 to <=500ms	1 (2.4%)	2 (4.9%)
>500ms	0 (0.0%)	1 (2.4%)
Subjects(filtered)	40 (95.2%)	41 (100.0%)
1stColItemSubjects	42 (100.0%)	41 (100.0%)

Source: JRevSelADSL307SAFFL_Y AVALCATbyTRT01AfiltPARAM_QTcF APERIODC_RCP

Table 104: QTcF, change from baseline, RCP, study 307

CHGCAT	PLACEBO	SA237
(missing)	39 (92.9%)	41 (100.0%)
>0 to <=30ms	23 (54.8%)	29 (70.7%)
>30 to <=60ms	5 (11.9%)	7 (17.1%)
>60ms	3 (7.1%)	4 (9.8%)
Subjects(filtered)	40 (95.2%)	41 (100.0%)
1stColItemSubjects	42 (100.0%)	41 (100.0%)

Source: JRevSelADSL307SAFFL_Y CHGCATbyTRT01AfiltPARAM_QTcF APERIODC_RCP

Reviewer Comment: Overall, there does not appear to be a significant cardiac safety concern associated with satralizumab-mwge treatment.

8.5.10 Immunogenicity

See the review by Clinical Pharmacology

8.6 Analysis of Submission-Specific Safety Issues

8.6.1 Injection-related reactions

Injection-related reactions (IRR) occurred 11 times in 7 subjects (9.5%) treated with placebo. Four of these events were either erythema or bruising at the injection site, one each was blood pressure decreased, burning sensation, dizziness, cold feeling, fever and a swollen mouth. All

were mild, non-serious and recovered. An IRR occurred 42 times in 13 subjects (12.5%) treated with satralizumab-mwge. One subject had 7 events, 2 had 6 and one had 5 events. Six events terms were headache, 5 in the same subject. Seven event terms were related to local injection site bruising, burning, or stinging (all in one subject) or redness (4 events in one subject). Other event terms include one of hypotension, hypertension, loose stools, nausea, rash, itching, flushing, fever, and various terms for swelling or edema. None were considered serious. Three were severe, 4 were moderate, and the remainder were mild.

Reviewer Comment: The number of events exaggerates the incidence of IRRs. The terms for these events do not suggest a serious concern, confirmed by the lack of any considered serious and only a few considered severe.

8.6.2 Infections

The analysis of infections for the individual trials and for the ISS are limited in numbers but do not reveal to date any opportunistic infections or an increase in infections due to encapsulated organisms.

8.7 Safety Analyses by Demographic Subgroups

Study 307

The population of anti-AQP4 seropositive adults was all female. The relatively low number of adverse events in any one group limits interpretation of an analysis of adverse events by subgroups. There does not appear to be an increased incidence of adverse events by SOC or preferred terms by race or baseline immunosuppressant treatment.

Study 309

There were only 11 males who were anti-AQP4 seropositive. The relatively low number of adverse events in any one group limits interpretation of an analysis of adverse events by subgroups. There does not appear to be an increased incidence of adverse events by SOC or preferred terms by sex or race.

8.8 Specific Safety Studies/Clinical Trials

Study SA-001JP was a single ascending dose study of SC SA 237 ranging from 30 mg to 240 mg. There were no SAEs. The most common AE was a decrease in fibrinogen levels in those treated with SA 237 at doses of 120 mg and 240 mg.

Study SA-105JP was a multiple dose study in patients with rheumatoid arthritis. Doses were 30, 60, and 120 mg SC for up to 32 weeks with no placebo arm, followed by a 32-week open label

extension. There were 11 subjects in each cohort. There was one SAE of interstitial lung disease and one of bronchopneumonia. There were 5 events with preferred terms all related to pneumonia that caused temporary suspension of dosing. The most common non-serious adverse events were upper respiratory infections. Low fibrinogen levels were not noted in this study.

8.9 Additional Safety Explorations

8.9.1 Human Carcinogenicity or Tumor Development

There have no studies of human carcinogenicity or tumor development. There was one subject treated with satralizumab-mwge with a report of a squamous cell carcinoma.

8.9.2 Human Reproduction and Pregnancy

There are no exposures to satralizumab-mwge in pregnant women.

8.9.3 Pediatrics and Assessment of Effects on Growth

There were no assessments of growth in the few pediatric subjects in study 307.

8.9.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no overdoses, reports of withdrawal, or reports of increased disease activity on withdrawal of satralizumab-mwge. Abuse potential was not studied.

8.10 Safety in the Postmarket Setting

8.10.1 Safety Concerns Identified Through Postmarket Experience

There is no marketing experience with the use of satralizumab-mwge.

8.10.2 Expectations on Safety in the Postmarket Setting

Safety concerns post-approval may be guided by the experience with tocilizumab (Actemra) and sarilumab (Kevzara), similar drugs with a comparable target. Actemra is approved for the treatment of Rheumatoid Arthritis (RA), Giant Cell Arteritis, Systemic Juvenile Idiopathic Arthritis, and Cytokine Release Syndrome. Kevzara is approved for the treatment of RA. All of these underlying disorders are likely to lead to a safety profile that will differ from that of satralizumab-mwge treatment of the NMOSD population. Nevertheless, the black box warning for Actemra does include serious infections. There should be surveillance for serious infections should Enspryng be approved. The warnings and precautions for Actemra include gastrointestinal perforations which were not seen in the satralizumab-mwge studies. There is a warning for hepatotoxicity, changes in neutrophils, platelets, lipids, and liver transaminases.

8.10.3 Additional Safety Issues From Other Disciplines

See Section 4.4.

8.11 Integrated Assessment of Safety

Pooling the safety populations from studies 309 and 307 may lead to misleading results because of the use of concurrent immunotherapy in study 307. Analysis of the pooled studies does not reveal any new safety concerns not identified in the analyses of the individual studies.

Serious adverse events

The SAEs from the ISS are listed in [Table 105](#). Infections remain the most common SAE in both treatment groups.

Table 105: SAEs by SOC, ISS

Body System or Organ Class	Dictionary Derived Term	PLACEBO	SA237
Blood and lymphatic system disorders	Anaemia macrocytic	0 (0.0%)	1 (1.0%)
	Autoimmune thrombocytopenia	1 (1.4%)	0 (0.0%)
	Leukopenia	1 (1.4%)	0 (0.0%)
	Lymphopenia	1 (1.4%)	0 (0.0%)
Cardiac disorders	Acute myocardial infarction	0 (0.0%)	1 (1.0%)
	Bradycardia	0 (0.0%)	1 (1.0%)
Eye disorders	Retinal vein thrombosis	1 (1.4%)	0 (0.0%)
	Visual impairment	0 (0.0%)	1 (1.0%)
Gastrointestinal disorders	Abdominal pain	1 (1.4%)	0 (0.0%)
	Enterocolitis	0 (0.0%)	1 (1.0%)
	Nausea	0 (0.0%)	1 (1.0%)
General disorders and administration site conditions	Hypothermia	0 (0.0%)	1 (1.0%)
	Non-cardiac chest pain	0 (0.0%)	1 (1.0%)
Infections and infestations	Appendicitis	1 (1.4%)	0 (0.0%)
	Cystitis	1 (1.4%)	0 (0.0%)
	Escherichia sepsis	1 (1.4%)	0 (0.0%)
	Influenza	0 (0.0%)	2 (2.0%)
	Pneumonia	0 (0.0%)	2 (2.0%)
	Pulmonary sepsis	0 (0.0%)	1 (1.0%)
	Pyelonephritis	0 (0.0%)	1 (1.0%)
	Upper respiratory tract infection	1 (1.4%)	0 (0.0%)
	Urinary tract infection	2 (2.9%)	1 (1.0%)
	Urosepsis	0 (0.0%)	1 (1.0%)
	Femur fracture	0 (0.0%)	1 (1.0%)
Injury, poisoning and procedural complications	Injury	0 (0.0%)	1 (1.0%)
	Radius fracture	0 (0.0%)	1 (1.0%)
	Spinal compression fracture	0 (0.0%)	1 (1.0%)
	Breast cancer	1 (1.4%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Hepatic cancer	1 (1.4%)	0 (0.0%)

Body System or Organ Class	Dictionary Derived Term	PLACEBO	SA237
Nervous system disorders	Cervical radiculopathy	1 (1.4%)	0 (0.0%)
	Neuromyelitis optica	1 (1.4%)	0 (0.0%)
	Tension headache	0 (0.0%)	1 (1.0%)
Psychiatric disorders	Mental status changes	0 (0.0%)	2 (2.0%)
	Suicide attempt	0 (0.0%)	1 (1.0%)
Renal and urinary disorders	Dysuria	1 (1.4%)	0 (0.0%)
Reproductive system and breast disorders	Cervical dysplasia	0 (0.0%)	1 (1.0%)
	Uterine polyp	1 (1.4%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Apnoea	0 (0.0%)	1 (1.0%)
	Pulmonary oedema	0 (0.0%)	1 (1.0%)
Subtotal	Subjects(filtered)	14 (20.3%)	19 (19.0%)
Total	1stCollItemSubjects	69 (100.0%)	100 (100.0%)

Source: JReviSS SeIADSLSAFFL_Y SOCbyAEDECODbyTRT01AfilTRTEMFL_Y PERIOD_RCP AESER_Y

For the population treated with satralizumab-mwge during the RCP and/or the OLE, there is no new safety concern not identified in the individual trials ([Table 106](#)).

Table 106: SAEs by SOC, ISS, all SA237

AEBODSYS	AEDECOD	SA237
Blood and lymphatic system disorders	Anaemia macrocytic	0 (0.0%)
Cardiac disorders	Acute myocardial infarction	1 (1.3%)
	Bradycardia	0 (0.0%)
Eye disorders	Glaucoma	1 (1.3%)
	Visual impairment	0 (0.0%)
Gastrointestinal disorders	Enterocolitis	0 (0.0%)
	Nausea	1 (1.3%)
General disorders and administration site conditions	Gait disturbance	1 (1.3%)
	Hypothermia	0 (0.0%)
	Non-cardiac chest pain	0 (0.0%)
Infections and infestations	Appendicitis	1 (1.3%)
	Cellulitis	1 (1.3%)
	Endocarditis	1 (1.3%)
	Enterocolitis infectious	1 (1.3%)
	Hepatitis E	1 (1.3%)
	Influenza	1 (1.3%)
	Pneumonia	0 (0.0%)
	Pulmonary sepsis	0 (0.0%)
	Pyelonephritis	0 (0.0%)
	Upper respiratory tract infection	1 (1.3%)
	Urinary tract infection	0 (0.0%)
	Urosepsis	1 (1.3%)
Injury, poisoning and procedural complications	Femur fracture	0 (0.0%)
	Injury	1 (1.3%)
	Post procedural haematoma	1 (1.3%)
	Radius fracture	0 (0.0%)
	Spinal compression fracture	1 (1.3%)

AEBODSYS	AEDECOD	SA237
	Upper limb fracture	1 (1.3%)
Musculoskeletal and connective tissue disorders	Systemic lupus erythematosus	1 (1.3%)
Nervous system disorders	Convulsion	1 (1.3%)
	Intracranial aneurysm	1 (1.3%)
	Parkinsonism	1 (1.3%)
	Tension headache	1 (1.3%)
Psychiatric disorders	Mental status changes	0 (0.0%)
	Suicide attempt	0 (0.0%)
Renal and urinary disorders	Dysuria	1 (1.3%)
Reproductive system and breast disorders	Cervical dysplasia	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Apnoea	0 (0.0%)
	Pulmonary oedema	1 (1.3%)
	Subjects(filtered)	16 (20.8%)
	1stCollItemSubjects	77 (100.0%)

Source: JReviSS SeIADSLSAFFL_Y SOCbyAEDECODbyTRT02AfiltAESER_Y APTFL_Y

The adverse events occurring in the pooled RCPs and occurring in 5% or more of the subjects in the satralizumab-mwge population are listed in [Table 107](#). No new safety concerns are identified in this population.

Table 107: TEAEs, ISS, 5% or more of SA237 population

Dictionary Derived Term	PLACEBO	SA237
Upper respiratory tract infection	12 (17.4%)	20 (20.0%)
Headache	8 (11.6%)	20 (20.0%)
Nasopharyngitis	8 (11.6%)	19 (19.0%)
Urinary tract infection	15 (21.7%)	18 (18.0%)
Nausea	5 (7.2%)	14 (14.0%)
Arthralgia	1 (1.4%)	14 (14.0%)
Pain in extremity	6 (8.7%)	10 (10.0%)
Rash	3 (4.3%)	10 (10.0%)
Fatigue	3 (4.3%)	9 (9.0%)
Back pain	8 (11.6%)	8 (8.0%)
Leukopenia	4 (5.8%)	8 (8.0%)
Pruritus	2 (2.9%)	8 (8.0%)
Depression	2 (2.9%)	7 (7.0%)
Hypercholesterolaemia	5 (7.2%)	6 (6.0%)
Oropharyngeal pain	4 (5.8%)	6 (6.0%)
Diarrhoea	3 (4.3%)	6 (6.0%)
Neutropenia	3 (4.3%)	6 (6.0%)
Insomnia	1 (1.4%)	6 (6.0%)
White blood cell count decreased	0 (0.0%)	6 (6.0%)
Hypoaesthesia	0 (0.0%)	6 (6.0%)
Constipation	9 (13.0%)	5 (5.0%)
Influenza	6 (8.7%)	5 (5.0%)
Anaemia	5 (7.2%)	5 (5.0%)
Cystitis	5 (7.2%)	5 (5.0%)

Dictionary Derived Term	PLACEBO	SA237
Lymphopenia	4 (5.8%)	5 (5.0%)
Dizziness	3 (4.3%)	5 (5.0%)
Blood creatine phosphokinase increased	3 (4.3%)	5 (5.0%)
Vomiting	3 (4.3%)	5 (5.0%)
Pharyngitis	3 (4.3%)	5 (5.0%)
Myalgia	2 (2.9%)	5 (5.0%)
Alanine aminotransferase increased	2 (2.9%)	5 (5.0%)
Vertigo	1 (1.4%)	5 (5.0%)
Oedema peripheral	0 (0.0%)	5 (5.0%)
Hypertension	0 (0.0%)	5 (5.0%)
Sinusitis	0 (0.0%)	5 (5.0%)
Musculoskeletal stiffness	0 (0.0%)	5 (5.0%)
Subjects(filtered)	64 (92.8%)	95 (95.0%)
1stColItemSubjects	69 (100.0%)	100 (100.0%)

Using the FDA/ODE1 custom grouping of MedDRA terms, the increased incidence of terms indicating joint pain is prominent, as it is in the analyses of the individual trials and the ISS ([Table 108](#)).

Table 108: TEAEs, RCP, ISS, FDA ODE1 custom groupings

Analysis Columns	PLACEBO n=74		SA237 n=104		SA237%- PBO%
	n	%	N	%	
arthralgia, arthritis, arthrosis	1	1.351	17	16.35	15
headache	8	10.81	23	22.12	11.3
dyspepsia, N, V, indigestion, epigastric pain, gastritis, duodenitis	6	8.108	20	19.23	11.1
URI, cold, rhinitis, upper resp tract infection, flu-like illness	21	28.38	41	39.42	11
leukopenia (neutropenia and/or lymphopenia)	10	13.51	24	23.08	9.56
rash, eruption, dermatitis	3	4.054	12	11.54	7.48
edema, non-pulmonary, fluid retention, overload	1	1.351	9	8.654	7.3
eye other	2	2.703	10	9.615	6.91
infection, all	40	54.05	63	60.58	6.52
Nausea, vomiting	6	8.108	15	14.42	6.31
insomnia, sleep disturbance, abnormal dreams	1	1.351	7	6.731	5.38
pruritis	2	2.703	8	7.692	4.99
depression	2	2.703	8	7.692	4.99
somnolence, fatigue, sedation	3	4.054	9	8.654	4.6
insomnia	1	1.351	6	5.769	4.42
allergic RXN, hypersensitivity	4	5.405	10	9.615	4.21
fracture	2	2.703	7	6.731	4.03
asthenia, fatigue, malaise, weakness, narcolepsy	5	6.757	11	10.58	3.82
dermatitis	1	1.351	5	4.808	3.46
vertigo; vestibular dysfunction	1	1.351	5	4.808	3.46
anemia	6	8.108	12	11.54	3.43

Analysis Columns	PLACEBO n=74		SA237 n=104		SA237%- PBO%
	n	%	N	%	
diarrhea, colitis, enteritis, proctitis, gastroenteritis, C-diff	6	8.108	12	11.54	3.43
urticaria	1	1.351	4	3.846	2.49
infection, bacterial	1	1.351	4	3.846	2.49
Myalgia, myositis, rhabdomyolysis	2	2.703	5	4.808	2.1

Source: Diff more than 2 Subset of ODE 1 analysis table.jmp

Laboratory Studies

There are no new concerns on analysis of the laboratory studies using the pooled populations from studies 309 and 307.

90-day safety update

At the time of the 90-day safety update the total exposure for all subjects treated was over 400 subject years ([Table 109](#)). There were 132 subjects with one year or more exposure. Infections remained the most common adverse and serious adverse events. All serious infections are listed in [Table 110](#).

Table 109: Exposure, all treated with SA237, 90-day safety update

N	AP04 (SA237 treatment period) years					
	Mean	Std Dev	Min	Max	Median	Sum
166	2.64	1.4	0.24	5.3	2.53	438

Summary of APTFL_Y Subset of ADSL safety update pooled lr.jmp

Table 110: All serious infections, all treated with SA237, 90-day safety update

AEDECOD	N*	Percent
Pneumonia	4	2.22
Influenza	3	1.67
Urinary tract infection	3	1.67
Urosepsis	2	1.11
Appendicitis	1	0.56
Cellulitis	1	0.56
Cystitis	1	0.56
Endocarditis	1	0.56
Enterocolitis infectious	1	0.56
Hepatitis E	1	0.56
Pulmonary sepsis	1	0.56
Pyelonephritis	1	0.56
Upper respiratory tract infection	1	0.56

Source: SOC_INFINF Subset of AESER_Y Subset of APTFL_Y Subset of ADAE 120 day pooled By (USUBJID, AEDECOD) NUSUBJID
By (AEDECOD).jmp
*: N = NUSUBJID

9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting is not recommended.

10 Labeling Recommendations

10.2 Prescription Drug Labeling

The indication should be limited to adult patients who are anti-AQP4 antibody seropositive.

10.3 Nonprescription Drug Labeling

N/A

11 Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not recommended.

12 Postmarketing Requirements and Commitments

Because of the relatively limited number of subjects exposed and the limited experience with long-term treatment, there should be a post-marketing requirement for a study of long-term safety with special attention to the incidence of infections.

Because the time course of the reduction in complement levels with prolonged treatment, there should be a post-marketing requirement for a study of complement levels with treatment durations significantly longer than those from the clinical trials.

13 Appendices

13.1 References

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13.2 Financial Disclosure

Covered Clinical Study (Name and/or Number): BN40898 and BN40900

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>745</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2 (one site)</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: <u>2</u> Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial	Yes ☒	No ☐ (Request details from Applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>742</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3 NMO/NMOSD diagnostic criteria

Wingerchuk, 2006²³

Definite NMO:

Optic neuritis

Acute myelitis

At least two of three supportive criteria

- o Contiguous spinal cord lesion identified on an MRI scan extending over 3 vertebral segments
- o Brain MRI not meeting diagnostic criteria for multiple sclerosis
- o NMO-IgG seropositive status

NMOSD

Seropositive for anti-AQP4-IgG

Idiopathic single or recurrent events of myelitis; ≥ 3 vertebral segments on spinal cord MRI

Optic neuritis, single, recurrent or simultaneous bilateral

13.4 Kurtzke Expanded Disability Status Scale

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory, and the precise step number is defined by the Functional System (FS) score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation, and usual equivalents in Functional System scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS. Each step (e.g., 3.0 to 3.5) is still part of the DSS scale equivalent (i.e., 3). Progression from 3.0 to 3.5 should be equivalent to the DSS score of 3.

- 0 - Normal neurological exam (all grade 0 in FS).
- 1.0 - No disability, minimal signs in one FS (i.e., grade 1).
- 1.5 - No disability, minimal signs in more than one FS (more than on FS grade 1).
- 2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1).
- 2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1).
- 3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.
- 3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1).
- 4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest 500 meters.
- 4.5 - Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance: characterized by relatively severe disability usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.
- 5.0 - Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions): (usual FS equivalents are one grade 5 alone, others 0 or 1: or combinations of lesser grades usually exceeding specifications for step 4.0).
- 5.5 - Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities: (usual FS equivalents are one grade 5 alone, others 0 or 1: or combination of lesser grades usually exceeding those for step 4.0).
- 6.0 - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting: (usual FS equivalents are combinations with more than two FS grade 3 +).
- 6.5 - Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting (usual FS equivalents are combinations with more than two FS grade 3 +).
- 7.0 - Unable to walk beyond approximately 5 meters even with aid, essentially restricted to a wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (usual FS equivalents are combinations with more than one FS grade 4 +; very rarely pyramidal grade 5 alone).
- 7.5 - Unable to take more than a few steps; restricted to wheelchair, may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair; (usual FS equivalents are combinations with more than one FS grade 4 +).

- 8.0 - Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day, retains many self-care functions; generally has effective use of arms; (usual FS equivalents are combinations, generally grade 4 + in several systems).
- 8.5 - Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions; (usual FS equivalents are combinations generally 4 + in several systems).
- 9.0 - Helpless bed patient: can communicate and eat; (usual FS equivalents are combinations, mostly grade 4 +).
- 9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow; (usual FS equivalents are combinations, almost all grade 4 +).
- 10.0 - Death due to MS.

13.5 Relapse criteria for a new or worsening neurologic deficit

1. An increase of at least 1.0 point on the EDSS score, or a 2.0-point increase if the baseline EDSS was zero
2. An increase of at least 2.0 points on one of the appropriate FSS
3. An increase of at least 1.0 point on two or more of the appropriate FSS if the baseline score was one or more
4. An increase of at least 1.0 point in single eye FSS when the baseline score in that eye was one or more.

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