Summary Table of Study Protocol

Title	*Real-world Persistency, Effectiveness, and Safety Among Patients with NMOSD Treated with Inebilizumab*
Protocol version identifier	20250110, V1.0
Date of last version of the protocol	08 January 2026
EU Post Authorization Study (PAS) Register No	N/A
Active Substance	Inebilizumab
Medicinal Product	N/A
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Product Reference	N/A
Procedure Number	N/A
Joint PASS	No
Research Question and Objectives	Inebilizumab demonstrated efficacy and safety for the treatment of Neuromyelitis Optica Spectrum Disorder (NMOSD) in multiple clinical trials (phase 2/3 N-Momentum trials). We seek to understand the real-world effectiveness and safety of inebilizumab for NMOSD among a cohort of NMOSD patients representing a broader range of comorbidities and disease severity. This study aims to assess persistence, time to attack, and annualized attack rate among patients with NMOSD treated with inebilizumab. We also aim to evaluate the rate of safety events of interest occurring while on inebilizumab treatment.
Country(ies) of Study	US
Author	PPD Amgen Inc. PPD Thermo Fisher Scientific

Marketing Authorization Holder

Marketing authorization holder(s)	Amgen, Inc.
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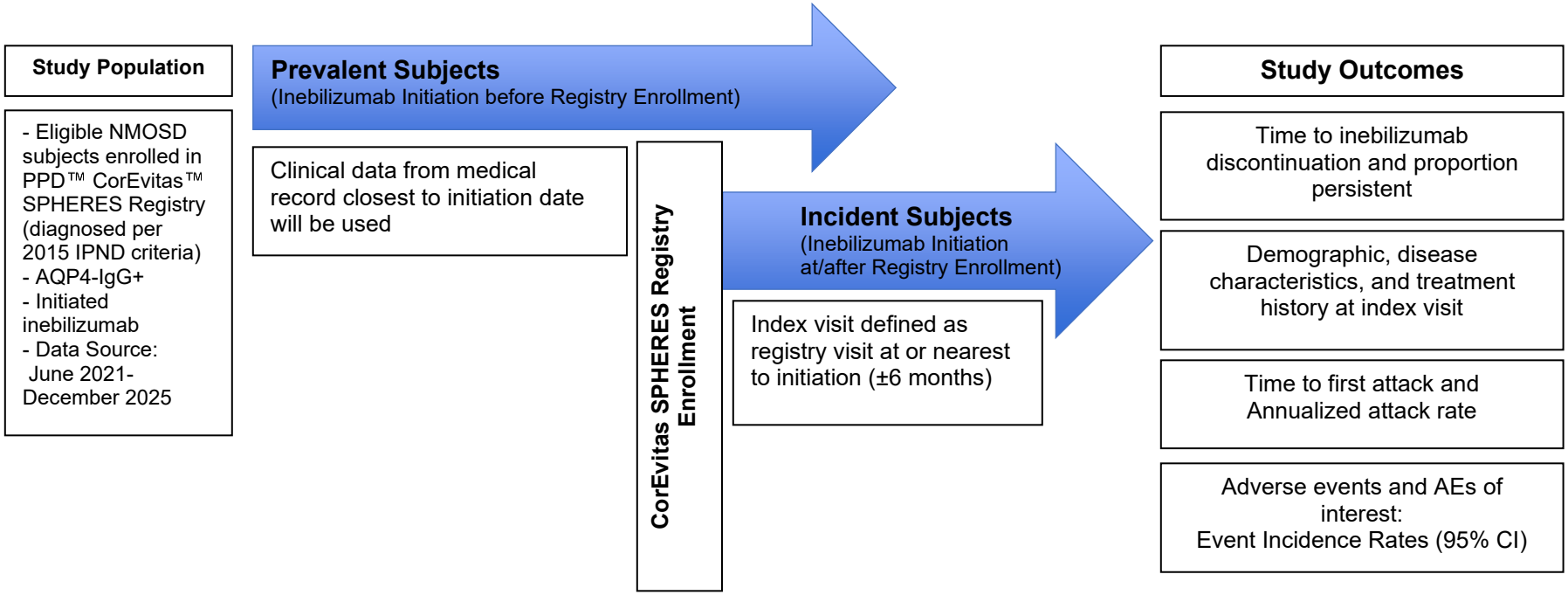
Study Design Schema



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2. List of Abbreviations

Abbreviation	Full Name
AAR	Annualized Attack Rate
AESI	Adverse Event of Special Interest
AHRQ	Agency for Healthcare and Research Quality
APS	Area Postrema Syndrome
BMI	Body Mass Index
CDM	Clinical Data Management
CI	Confidence Interval
ClinRO	Clinician Reported Outcome
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
EAIR	Exposure Adjusted Incidence Rate
EIR	Event Incidence Rate
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale
EQ-5D-5L	EuroQol 5 Dimensions 5 Level Version
EQ-VAS	EuroQol Visual Analog Scale
GERD	Gastroesophageal Reflux Disease
GPP	Good Pharmacoepidemiology Practices
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IPND	International Panel for NMO Diagnosis
IRB	Institutional Review Board
IST	Immunosuppressant Therapy
ITP	Idiopathic Thrombocytopenic Purpura
IVIG	Intravenous Immunoglobulin
KM	Kaplan-Meier
LFT	Liver Function Test
MFIS	Modified Fatigue Impact Scale
NASH	Non-alcoholic Steatohepatitis
NMOSD	Neuromyelitis Optica Spectrum Disorder
NMSC	Non-melanoma Skin Cancer
NRS	Numeric Rating Scale
PD-Q	PainDETECT Questionnaire
PHQ	Patient Health Questionnaire
PII	Personally Identifiable Information
PRO	Patient-Reported Outcome
PY	Person-years
Q1	Quartile 1 (25th percentile)
Q3	Quartile 3 (75th percentile)

RMP	Registry Monitoring Plan
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-MPQ-2	Short-Form McGill Pain Questionnaire-2
SOPs	Standard Operating Procedures
SPHERES	Synergy of Prospective Health & Experimental Research for Emerging Solutions
TAE	Targeted Adverse Event
ULN	Upper Limit of Normal
US	United States
VA	Veterans Affairs
VFQ-UI	Visual Function Questionnaire - Utility Index

3. Responsible Parties

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Thermo Fisher Scientific: PPD

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4. Abstract

- **Study Title**

Real-world Persistency, Effectiveness, and Safety Among Patients with NMOSD Treated with Inebilizumab

- **Study Background and Rationale**

(NMOSD) are rare autoimmune disorders of the central nervous system (CNS) that predominantly affect the optic nerves and spinal cord [1, 2]. Prolonged periods without treatment can lead to disability via attacks, so early initiation of immunosuppressive therapy is recommended to prevent NMOSD attack [3]. In recent years, biologic therapies were approved for prevention of NMOSD attacks in patients with antibodies against aquaporin-4 (AQP4-IgG+). These include eculizumab, inebilizumab, ravulizumab, and satralizumab, with all showing clear benefit in preventing relapse in placebo-controlled trials.

Inebilizumab targets the CD19 monoclonal antibody, effectively depleting circulating B cells and significantly reducing NMOSD attack risk and disability progression in AQP4-antibody seropositive patients [4]. In the phase 2/3 N-MOmentum clinical trial, inebilizumab reduced the risk of NMOSD attacks compared with placebo in AQP4-antibody seropositive patients. Real-world data, which would support results from clinical trials in a broader, more diverse population of NMOSD patients are lacking.

This study aims to characterize therapy persistence, effectiveness, and incidence of safety events of interest among subjects with NMOSD who are enrolled in the PPD™ CorEvitas™ Synergy of Prospective Health & Experimental Research for Emerging Solutions (SPHERES) Registry and are treated with inebilizumab.

- **Study Feasibility and Futility Considerations**

Registry data as of October 31, 2025 was used for study feasibility. There were a total of 74 subjects diagnosed with NMOSD according to the 2015 International Panel for NMO Diagnosis (IPND) consensus diagnostic criteria who initiated inebilizumab prior to, at, or after enrollment

into the CorEvitas SPHERES Registry. Of those, 69 are AQP4-IgG+ with 50 (72%) initiating inebilizumab prior to enrollment and 19 (28%) initiating inebilizumab at, or after enrollment.

- **Research Question and Objective(s)**

Objectives	Endpoints
Primary	
1. To estimate persistence of inebilizumab use among subjects with NMOSD in the CorEvitas SPHERES Registry 2. To estimate the time to first attack and annualized attack rate of NMOSD in subjects while treated with inebilizumab. Objectives 1 and 2 will be stratified by first-line, second-line, and third-line or higher inebilizumab use. (If subgroup sample size<11, the categories will be collapsed into first-line vs. second-line or higher). 3. To estimate the exposure adjusted incidence rate (EAIR) of adverse events (AEs) and adverse events of special interest (AESIs) and the event incidence rate (EIR) for AESIs in subjects while treated with inebilizumab.	1. Time from inebilizumab initiation to physician reported date of discontinuation of inebilizumab 2. Time from inebilizumab initiation to first attack, total attacks, annualized attack rate. 3. EAIR for AEs and AESIs, and EIR for AESIs, adjusted by person-years.
Exploratory	
CCI [redacted]	

- **Hypothesis(es)/Estimation**

As a descriptive study, no a priori hypotheses will be tested. However, we expect that real world evidence on inebilizumab safety will be generally comparable to findings from clinical trials.

- **Study Design/Type**

This is a descriptive longitudinal study of subjects diagnosed with NMOSD enrolled in the CorEvitas SPHERES Registry from June 2, 2021 to December 31, 2025 or most recent data as of protocol approval date.

- **Study Population or Data Resource**

Data from the CorEvitas SPHERES Registry will be used for this study. The CorEvitas SPHERES Registry (as of June 30, 2025) has enrolled 485 subjects with NMOSD from 30 private and academic clinical sites with 84 physicians throughout 21 states in the United States (US). The population for this study will include subjects with registry visits from June 2, 2021 to December 31, 2025 or the most recent data as of protocol approval date.

- **Summary of Subject Eligibility Criteria**

1. Adult subjects enrolled in the CorEvitas SPHERES Registry
2. Initiated inebilizumab either prior to, at, or after enrollment into the CorEvitas SPHERES Registry
3. AQP4-IgG+ serostatus

Variables

Outcome Variable(s)

Primary Objective 1: Persistence of inebilizumab

- Time in months from date of physician reported inebilizumab initiation to date of discontinuation of inebilizumab
- As a part of this objective, we will also describe inebilizumab initiators at the index visit
- Description of Patient Characteristics at inebilizumab initiation:
  - Sociodemographic Characteristics
    - Age
    - Sex
    - Race (White, Black, Asian, Other)
    - Ethnicity (Hispanic or non-Hispanic)
    - Body mass index (BMI)
    - Type of health insurance plan (Private, Medicare, Medicaid, Military/VA)
  - History of Comorbidities
    - Autoimmune condition
    - Cancer / Malignancy event
    - Cardiovascular / Circulatory event

- Gastrointestinal event
- Hepatic event or condition
- Metabolic Condition
- Neurologic event or condition
- Anxiety
- Depression
- Respiratory Condition
- History of Serious Infections
    - Cellulitis, Herpes zoster, Otitis, Sinusitis, Upper respiratory infection, Bronchitis, Pneumonia, Tuberculosis (active), COVID-19, Gastroenteritis, Diverticulitis, Urinary tract infection, Osteomyelitis, Meningitis / encephalitis, Endophthalmitis, Lyme disease, HIV/AIDS, Hepatitis B, Hepatitis C, Other viral hepatitis, Progressive Multifocal Leukoencephalopathy, Sepsis, Other infection

- CorEvitas SPHERES Registry Disease Characteristics
    - Newly diagnosed (within 1 year)
    - Time since symptom onset (years)
    - Time since diagnosis (years)
    - Diagnosed with NMOSD at time of first neurological episode
    - Phenotype of first neurological episode
        - Optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic syndrome, symptomatic cerebral syndrome
    - Number of attacks (including the initial episode) prior to index visit
        - Continuous
        - Categorical: 1, 2, 3+
    - Manifestations of previous attacks (including the initial episode) prior to index visit
        - Optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic syndrome, symptomatic cerebral syndrome
- CorEvitas SPHERES Registry Clinician Reported Outcome (ClinRO) Measures
    - Expanded Disability Status Scale (EDSS)
- Patient-Reported Outcome (PRO) Measures
    - Modified Fatigue Impact Scale (MFIS)
    - PainDETECT Questionnaire (PD-Q)

- Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2)
- Pain Severity Numeric Rating Scale (NRS)
- Visual Function Questionnaire - Utility Index (VFQ-UI)
- EuroQol - Visual Analog Scale (EQ-VAS)
- EQ-5D-5L Health Status (EQ-5D-5L)
- Patient Health Questionnaire-2 (PHQ-2)

▪ Medications for NMOSD

- Previous therapies (treatment started before inebilizumab initiation date)
- Concomitant therapies (treatment in use and newly started/prescribed at initiation date)

Primary Objective 2: Time to first attack and annualized attack rate

- Time in months from date of physician reported inebilizumab initiation to first NMOSD attack
- Annualized attack rate: total number of attacks divided by the number of person-years (PY) on therapy, overall and on yearly basis

Primary Objective 3: Incidence of adverse events and adverse events of special interest

- Number (%) of subjects with adverse events (AE) and adverse events of special interest (AESI)
- Exposure adjusted incidence rate adjusted by person-years for AEs and AESIs
- Event incidence rate adjusted by person-years for AESIs

- **Exposure Variable(s)**

  Time on inebilizumab treatment (as a single arm study, this is the only exposure)

Other Covariate(s)

N/A

- **Study Sample Size**

  CorEvitas SPHERES Registry data as of October 31, 2025 was used for study feasibility. There are a total of 69 subjects diagnosed with NMOSD according to the 2015 International Panel for Neuromyelitis Optica Diagnosis (IPND) consensus diagnostic criteria who are AQP4-IgG+ and initiated inebilizumab prior to, at, or after enrollment into the CorEvitas SPHERES Registry. Of those, 50 (72%) initiated inebilizumab prior to enrollment and 19 (28%) initiated inebilizumab at or after enrollment.

- **Data Analysis**

  Descriptive summary statistics, including means and standard deviation (SD), for continuous variables, and counts and percentages for categorical variables, will be reported for each of the sociodemographic, disease, comorbidity, treatment history, and disease severity measures at the index visit.

  Kaplan-Meier (KM) methodology will be used to assess time to inebilizumab discontinuation and time to first attack. Annualized attack rates and corresponding 95% confidence intervals (CIs) will be estimated.

  AEs and AESIs will be summarized for subjects who initiate inebilizumab prior to, at, or after registry enrollment. EAIRs of AEs and AESIs will be computed as the number of subjects experiencing at least one occurrence of the event divided by the total person-years at risk and expressed per 100 person-years. The event incidence rate (EIR) adjusted by person-years will be computed for AESIs using a negative binomial model adjusted for individual exposure time and scaled to 100 PY. For all safety analyses, all events within subject for each individual event type will be included.

5. Amendments and Updates

None

6. Rationale and Background

Neuromyelitis Optica Spectrum Disorder (NMOSD) is a rare autoimmune disorder of the central nervous system (CNS) that predominantly affects the optic nerves and spinal cord [1, 2]. Worsening of symptoms can lead to disability, so early initiation of immunosuppressive therapy is recommended to reduce NMOSD relapses [3]. Further, studies suggest that continuing therapy, even during extended relapse-free periods, is beneficial [5, 6].

Current treatments for NMOSD include therapies for managing attacks, such as corticosteroids and plasmapheresis, and for maintenance therapy, such as immunosuppressants (azathioprine and mycophenolate mofetil) and rituximab. While these therapies can be effective and are generally well-tolerated, long-term use—particularly of immunosuppressants—may lead to an increased risk of infections, and corticosteroids carry additional risks, such as osteoporosis and metabolic complications [7]. Newer biologic therapies approved for prevention of NMOSD relapses in patients with antibodies against aquaporin-4 (AQP4-IgG+) include eculizumab, inebilizumab, ravulizumab, and satralizumab.

Inebilizumab targets the CD19 monoclonal antibody, effectively depleting circulating B cells and significantly reducing NMOSD attack risk and disability progression among AQP4-IgG seropositive patients [4]. In the phase 2/3 N-MOmentum clinical trial, inebilizumab demonstrated a clear benefit in preventing relapses compared with placebo, with sustained efficacy observed in long-term extension studies. Treatment was generally well tolerated, with most adverse events being of mild to moderate severity. While clinical trials have established the efficacy and general safety of inebilizumab, real-world data, reflecting its effectiveness and safety in a broader, more diverse population of NMOSD patients are limited.

This study aims to characterize therapy persistence and rate of attacks of subjects with NMOSD who are enrolled in the CorEvitas Synergy of Prospective Health & Experimental Research for Emerging Solutions (SPHERES) Registry and are treated with inebilizumab.

6.1 Diseases and Therapeutic Area

NMOSD is a rare autoimmune disorder causing relapsing inflammation of the optic nerves and spinal cord. Inebilizumab (UPLIZNA®) is an anti-CD19 monoclonal antibody that depletes B cells involved in NMOSD pathogenesis. It is indicated for adults with AQP4-IgG+ NMOSD and administered as 300 mg IV every six months after two loading doses.

6.2 Rationale

N/A

6.3 Feasibility and Futility Considerations

Registry data as of October 31, 2025 was used for study feasibility. There are a total of 69 subjects diagnosed with NMOSD according to the 2015 International Panel for NMO Diagnosis (IPND) consensus diagnostic criteria who are AQP4-IgG+ and initiated inebilizumab prior to, at, or after enrollment into the CorEvitas SPHERES Registry. Of those, 50 (72%) initiated inebilizumab prior to enrollment and 19 (28%) initiated inebilizumab at or after enrollment.

6.4 Statistical Inference (Estimation or Hypothesis[es])

There are no *a priori* hypotheses for this descriptive analysis. The 95% confidence intervals (CIs) will be reported for variables where appropriate.

7. Research Question and Objectives

This study leverages data from the CorEvitas SPHERES Registry for NMOSD to estimate the persistence of inebilizumab therapy, effectiveness, and safety events of interest among

a real-world cohort of patients with NMOSD. These findings may provide insights for clinicians, payers, and other healthcare professionals, as real-world evidence on the performance of inebilizumab can support more informed treatment strategies and improve patient outcomes.

7.1 Primary Objectives

1. To estimate the persistence of inebilizumab use among subjects with NMOSD in the CorEvitas SPHERES Registry.

2. To estimate the time to first attack and annualized attack rate (AAR) of NMOSD in subjects while treated with inebilizumab.

Objectives 1 and 2 will be stratified by first-line, second-line, and third-line or higher use.

3. To estimate the exposure adjusted incidence rate (EAIR) of AEs and AESIs, and the event incidence rate (EIR) of AESIs while treated with inebilizumab.

7.2 Exploratory Objective

CCI [redacted]

8. Research Methods

8.1 Study Design

This longitudinal, exploratory study uses data from the CorEvitas SPHERES Registry to evaluate real-world persistence, effectiveness, and safety of inebilizumab in adults with NMOSD. Descriptive statistics will summarize patient demographics, disease characteristics, and treatment history at index visit. Time to discontinuation (persistence) and time to first attack will be analyzed using Kaplan-Meier (KM) method. Annualized attack rates and event incidence rates of safety events of interest will be calculated per person-year (PY) with corresponding 95% CIs. This design enables assessment of treatment outcomes in real-world clinical practice, though representativeness may be limited and retrospective data abstraction may limit completeness and generalizability.

8.1.1 Chart Abstraction

Subjects who initiated inebilizumab prior to CorEvitas SPHERES Registry enrollment (referred to as “prevalent subjects”) will not have registry data collected at the time of treatment initiation, as this occurred before enrollment. To ensure that subjects with inebilizumab initiation before registry enrollment are included in the analyses, site facilitators will retrospectively review medical records to obtain patient information from the clinical visit

closest to inebilizumab initiation. If any NMOSD attack events occurred during the period between inebilizumab initiation and registry enrollment, sites were instructed to retrieve information related to those attack events from available medical records.

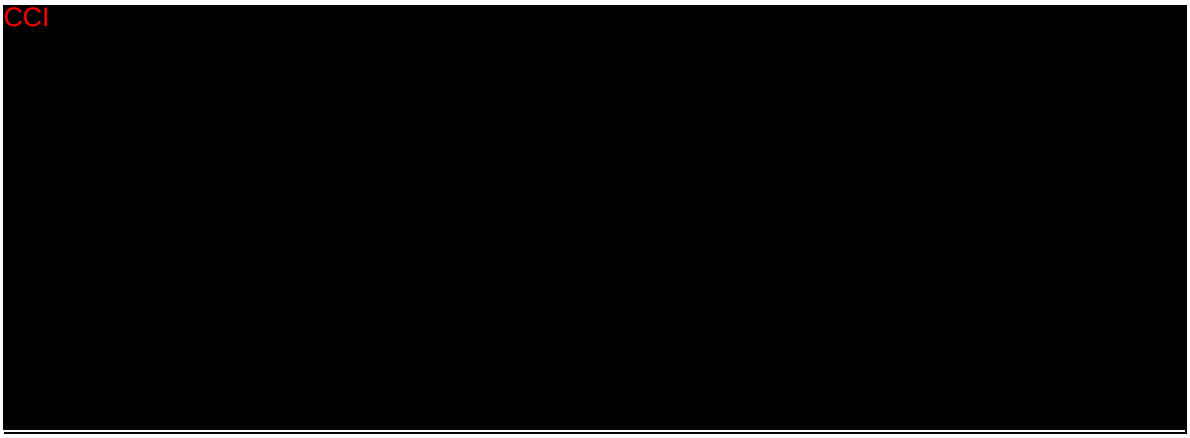
For adverse events and comorbidities that may occur during the period prior to enrollment, chart abstraction is limited to the review of AEs collected at the time of registry enrollment. Site facilitators provide any updates if information available in the medical records differs from what was reported at enrollment. Therefore, typical measures collected, and reviews conducted for AEs occurring after enrollment (see section 8.7.2), such as information obtained through Targeted Adverse Event (TAE) forms, are not available for pre-enrollment events.

During chart abstraction, exact patient-reported outcome (PRO) measures may not be available if they were not collected as part of routine standard-of-care visits. In such cases, comparable clinical or functional assessment elements documented in the medical record will be identified and used in place of the missing PRO measures, if available.

The table below lists the elements that will be retrieved during the chart abstraction process at the time of inebilizumab initiation and at the time of attack.

Table 8.1.1. Data elements for chart abstraction

Inebilizumab initiation	Data element to retrieve
Relapses	Has the subject had a relapse prior to drug initiation?
Weight	Weight at visit
Comorbidities and AEs	Current comorbidity & AEs, and date of onset for each
	Infections
Diagnostics	Recent Lab-imaging results
	Autoimmune panel
Health Insurance	Does the patient have health insurance, all types that apply
PROs: QoL	EQ VAS
PROs: Fatigue	Fatigue
PROs: Visual	Visual function: VFQ-25
PROs: Pain	PainDETECT Questionnaire (PD-Q)
Confirm NMOSD maintenance therapy	Biologics, immunosuppressants, other and corticosteroids
Concurrent Medications	Medications for: Anxiety/depression, Blood pressure, Bladder dysfunction, Fatigue, Spasticity, Pain, and Other
CCI	[redacted]



8.2 Setting and Study Population

The CorEvitas SPHERES Registry for NMOSD is a prospective, multicenter, observational research study of subjects with NMOSD under the care of a neurologist. The CorEvitas SPHERES Registry was established in June 2021 in collaboration with The Guthy-Jackson Charitable Foundation, academic and community neurology practitioners, industry sponsors and patients to facilitate closing gaps in information and understanding of NMOSD. Longitudinal follow-up data is collected from both subjects and providers during routine clinical encounters using CorEvitas SPHERES Registry questionnaires. Data collected includes subject demographics, lifestyle characteristics, disease duration, medical history (including all prior and current treatments for NMOSD), disease activity and severity, other clinician- and patient-reported outcomes, comorbidities and adverse events, infections, and other targeted safety outcomes. Blood collection and other diagnostic tests are not required for participation; however, relevant standard of care laboratory and imaging results are reported when available.

To be eligible for enrollment into the CorEvitas SPHERES Registry, a subject must satisfy all of the inclusion criteria and none of the exclusion criteria listed below**:**

SPHERES Registry Inclusion Criteria

- Be diagnosed with NMOSD according to the 2015 IPND consensus diagnostic criteria
- Be at least 18 years of age or older (age ≥18 years)
- Be willing to provide Personal Information

SPHERES Registry Exclusion Criteria

- Unable or unwilling to provide informed consent to participate in the registry

- Unable or unwilling to provide Personally Identifiable Information (PII)
- Had a clinically confirmed NMOSD neuro-episode within the 12 weeks prior to enrollment.
- Is participating or planning to participate in a double-blind randomized trial for an NMOSD drug. Note: Concurrent participation in another observational registry or open label Phase 3b/4 trial is allowed.

8.2.1 Study Period

Data obtained from the CorEvitas SPHERES Registry among subjects who enrolled from June 2, 2021 to December 31, 2025 (or data available as of the protocol approval date). Data obtained via chart abstraction will be used for the subset of subjects who initiated inebilizumab prior to CorEvitas SPHERES Registry enrollment and includes the period starting at the date of inebilizumab initiation.

8.2.2 Subject Eligibility

8.2.2.1 Inclusion Criteria

To be included in this study, subjects from the CorEvitas SPHERES Registry must meet the following criteria:

1. Enrolled in the CorEvitas SPHERES Registry
2. Initiated inebilizumab either prior to, at, or after enrollment into the CorEvitas SPHERES Registry
3. Is AQP4-IgG+ seropositive

8.2.2.2 Exclusion Criteria

- Subjects who are not AQP4-IgG+ seropositive
- Subjects with inebilizumab start and discontinuation on the same date. This situation may occur when a subject does not return after the first study visit and no subsequent dosing, follow-up, or discontinuation documentation is available; in such cases, the most recent on study drug log attestation date may be identical to the first (and only) visit date, resulting in an apparent same-day initiation and discontinuation.

8.2.3 Matching

N/A

8.2.4 Baseline Period

The CorEvitas SPHERES Registry is an observational registry and therefore collects data from subjects and physicians when subjects attend routine visits. Unlike clinical studies, visits are not timed with exactly uniform spacing. Thus, time period definitions for the current study need to accommodate this unique feature of observational registries.

A registry visit is a clinical visit scheduled by a physician as part of routine care with a neurologist or qualified physician extender at which subject characteristics and clinical and PRO measures are assessed.

An initiation date is the date of a physician documented inebilizumab initiation. The initiation date might coincide with a registry visit but can also be reported before registry enrollment or between clinical registry visits.

An *index visit* is a registry visit corresponding to the inebilizumab initiation date. When inebilizumab is initiated at a registry visit, the date of the index visit is the initiation date. When inebilizumab is initiated after enrollment but not at a registry visit, the index visit is defined as the registry visit closest to the initiation, provided that the registry visit is within 6 months (183 days) before or after the initiation date. When inebilizumab is initiated prior to CorEvitas SPHERES Registry enrollment, the index visit is defined using the clinical visit (not registry visit) at the time of inebilizumab initiation, retrospectively collected using data abstraction.

8.2.5 Study Follow-up

The follow-up period, calculated in months, is the period beginning at the date of initiation to the date of physician reported inebilizumab discontinuation. Subjects with no reported drug stop will be considered to be on inebilizumab treatment and censored at the last date of on-study drug log attestation or, if available, the most recent drug entry recorded on a TAE form or Relapse form. Temporary interruptions of ≤90 days will be permitted, provided no new biologic therapy is initiated during that period.

8.3 Variables

8.3.1 Exposure Assessment

Initiation of inebilizumab (as a single arm study, this is the only exposure).

8.3.2 Outcome Assessment

8.3.2.1 Primary Objective 1: Persistence of Inebilizumab

Time to inebilizumab discontinuation will be computed as the months from inebilizumab initiation to discontinuation. Subjects with no reported drug stop will be considered to be on inebilizumab treatment and censored at the last date of on-study drug log attestation or, if available, the most recent drug entry recorded on a TAE form or Relapse form. Temporary interruptions of ≤90 days will be permitted, provided no new biologic therapy is initiated during that period.

8.3.2.2 Description of Patient Characteristics at Index Visit

* Asterisks denote measures available through chart abstraction.

- Sociodemographic Characteristics
  - Age at visit
  - Sex (male, female)
  - Race (White, Black/African American, Asian, Other)
  - Ethnicity (Hispanic or non-Hispanic)
  - Body weight (lbs)*
  - Body mass index (BMI) (Normal/underweight <25, Overweight 25 to <30, Obese ≥ 30)
  - Education (less than high school, High school graduate, diploma, or equivalent, some college/associate's/trade, college graduate or higher)
  - Type of health insurance plan (Private, Medicare, Medicaid, Military/VA)*
  - History of Comorbidities*
    - Autoimmune Condition[1]
    - Cancer / Malignancy Event[2]
    - Cardiovascular / Circulatory Event[3]
    - Gastrointestinal Event[4]
    - Hepatic Event or Condition[5]
    - Metabolic condition[6]
    - Neurologic Event or Condition[7]
    - Anxiety
    - Depression
    - Respiratory Condition[8]

[1] Autoimmune Events or Conditions include Autoimmune thyroid disease/Hashimoto's disease, Sarcoidosis, Vasculitis, Multiple sclerosis, Myasthenia gravis, Psoriasis, Psoriatic arthritis, Rheumatoid arthritis, Sjögren's syndrome, Systemic lupus erythematosus, Crohn's disease, Ulcerative colitis, Antiphospholipid syndrome, Pernicious anemia, Idiopathic thrombocytopenic purpura (ITP), diabetes mellitus Type 1, Other autoimmune condition
[2] Cancer / Malignancy Events include Breast cancer, Lung cancer, Colon cancer, Uterine cancer, Cervical cancer, Prostate cancer, Leukemia, Lymphoma, Non-melanoma skin cancer (basal cell), Non-melanoma skin cancer (squamous cell), Melanoma skin cancer, Multiple myeloma, Pre-malignancy, Paraneoplastic syndrome, Other cancer
[3] Cardiovascular/Circulatory Events include Coronary artery bypass graft, Coronary angioplasty w/wo cardiac stent, Cardiac arrhythmia non-serious, Myocardial infarction, Unstable angina, Coronary artery disease non-serious, Congestive heart failure (non-serious), Congestive heart failure (serious), Stroke, Transient ischemic attack, Other cardiac condition (serious), Other cardiac condition (non-serious), Deep vein thrombosis, Pulmonary embolism, Other venous thromboembolism, Other vascular condition (serious), Other vascular condition (non-serious)
[4] Gastrointestinal Events include GERD/acid reflux, Gastrointestinal perforation, Other gastrointestinal disorder(non-serious)
[5][5] Hepatic Events or Conditions include Fatty liver disease/NASH, Hepatic event (requiring biopsy or serious), Hepatic event (increased LFT's >3x ULN), Drug induced liver injury (serious), Other hepatic event (non-serious)
[6] Metabolic includes Hypertension, hyperlipidemia, diabetes mellitus Type 1 and II, osteoporosis, other metabolic condition
[7] Neurologic Events or Conditions include Seizure(s), Progressive Multifocal Leukoencephalopathy, Multiple sclerosis, Other neurological disorder
[8] Respiratory Condition include Asthma, Chronic obstructive pulmonary disease (COPD), Interstitial lung disease/pulmonary fibrosis, Other respiratory condition

- History of Serious Infections[9]

- CorEvitas SPHERES Registry Disease Characteristics
  - Newly diagnosed (within 1 year)
  - Time since symptom onset (years)
  - Time since diagnosis (years)
  - Diagnosed with NMOSD at time of first neurological episode
  - Phenotype of first neurological episode
    - Optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic syndrome, symptomatic cerebral syndrome
  - Number of previous attacks (including the initial episode) prior to index visit*
    - Continuous
    - Categorical: 1, 2, 3+
  - Manifestations of previous attacks (including the initial episode) prior to index visit*
    - Optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic syndrome, symptomatic cerebral syndrome
- Medications for NMOSD*
  - Previous therapies (treatment started before initiation date)
    - Rituximab
    - Approved for NMOSD biologic (eculizumab, satralizumab, ravulizumab)
    - Not approved for NMOSD biologic (ocrelizumab, ofatumumab, sarilumab, tocilizumab)
  - Immunosuppressant Therapy (IST): (azathioprine, cyclophosphamide, cyclosporine, dimethyl fumarate, diroximel fumarate, fingolimod, leflunomide, cladribine, methotrexate, monomethyl fumarate, mycophenolate mofetil, siponimod, tacrolimus, teriflunomide, mitoxantrone)
  - Glucocorticoids (GS): (dexamethasone, methylprednisolone, prednisolone, prednisone)
  - Immunoglobulin (IVIG) Therapy
  - Other (glatiramer acetate, sulfasalazine, hydroxychloroquine, other)
    - Concomitant therapies (treatment in use and newly started/prescribed at initiation date)
    - GS, IST, Other

[9] Serious Infections include Cellulitis, Herpes zoster, Otitis, Sinusitis, Upper respiratory infection, Bronchitis, Pneumonia, Tuberculosis (active) COVID-19, Gastroenteritis, Diverticulitis, Urinary tract infection, Osteomyelitis, Meningitis / encephalitis, Endophthalmitis, Lyme disease, HIV/AIDS Hepatitis B, Hepatitis C, Other viral hepatitis, Progressive Multifocal Leukoencephalopathy, Sepsis, Other infection

- PRO Measures
  - Modified Fatigue Impact Scale (MFIS)*
  - PainDETECT Questionnaire (PD-Q)*
  - EuroQol - Visual Analog Scale (EQ-VAS)*
  - Visual Function Questionnaire - Utility Index (VFQ-UI)*
  - EQ-5D-5L Health Status (EQ-5D-5L)
  - Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2)
  - Pain Severity Numeric Rating Scale (NRS)
  - Patient Health Questionnaire-2 (PHQ-2)
- Clinician Reported Outcome Measures
  - Expanded Disability Status Scale (EDSS)

8.3.2.3 Primary Objective 2: Time to First Attack and Annualized Attack Rate

An attack is defined as the onset or worsening of neurological symptoms consistent with NMOSD that is assessed by the provider and confirmed as an attack following patient report of possible new or worsening symptoms.

Time to first attack (in months) will be measured from the date of inebilizumab initiation to date of discontinuation. To account for the drug's elimination and potential residual biologic effect (half-life ≈18 days), a 3-month risk extension period (calculated as 5 times the half-life of 18 days) following discontinuation will be included in the exposure window [8]. Any attack occurring during this risk extension period will be considered an event. For subjects without a reported discontinuation, exposure time will be censored at the date of the most recent date of on-study drug log attestation or, if available, the most recent drug entry recorded on a TAE form or Relapse form.

To calculate the annualized attack rate, attack events and exposure time will be treated as follows:

- If a subject experiences an attack event and does not discontinue treatment after the attack, the exposure time for that subject will be censored for a 30-day period beginning on the date of the attack.
- Any additional attack events occurring during this 30-day period will be assigned to the initial attack event and not considered a new attack. Exposure time will resume on the 31st day following the attack event date, continuing until the end of the risk extension period (if discontinuation occurs), or to the date of the final on-study drug log attestation date (if no discontinuation is reported) or, if available, the most recent drug entry recorded on a TAE form or Relapse form.

8.3.2.4 Primary Objective 3: Incidence of Adverse Events and Events of Special Interest

Adverse events are ascertained from Provider Follow-up Questionnaires and/or TAE Questionnaires (for adverse events that are serious and/or for registry-defined safety events of interest). At enrollment and registry follow-up visits, providers assess subjects for adverse events using structured AE/comorbidity checklists and detailed infection fields, allowing systematic capture of metabolic, cardiovascular/vascular, infectious, respiratory, gastrointestinal/hepatic, autoimmune, neurologic/psychiatric, musculoskeletal, hematologic, malignancy, hypersensitivity, and other clinically relevant events (Table 8.3.2.4).

Table 8.3.2.4. Adverse Events assessed at registry visits

AE Category	Adverse Event
Metabolic	Hypertension; Hyperlipidemia; Diabetes (Type I/II); Osteoporosis; Other metabolic conditions
Cardiovascular / Circulatory	CABG; Coronary angioplasty with or w/o stent; Arrhythmia; Myocardial infarction; Unstable angina; Coronary artery disease; Congestive heart failure; Stroke; TIA; Deep vein thrombosis; Pulmonary embolism; Other cardiac/vascular conditions
Allergies / Reaction / Drug Hypersensitivity	Mild/moderate drug hypersensitivity; Severe hypersensitivity (including infusion-related reactions); Anaphylaxis; Other serious allergies
Respiratory	Asthma (allergic); COPD; Interstitial lung disease/pulmonary fibrosis; Other respiratory conditions
Malignancies	Breast, lung, colon, uterine, cervical, prostate cancers; Leukemia; Lymphoma; Multiple myeloma; Melanoma; Non-melanoma skin cancer (basal and squamous cell); Other malignancies
Gastrointestinal / Hepatic	GERD/acid reflux; GI perforation; Other GI disorders; Fatty liver/NASH; Elevated LFTs >3x ULN; Drug-induced liver injury (DILI); Other hepatic events
Neurologic / Psychiatric	Seizures; Anxiety; Depression; Other neurologic or psychiatric conditions
Musculoskeletal	Fractures; Other musculoskeletal conditions
Autoimmune Conditions	Autoimmune thyroid disease/Hashimoto's disease; Sarcoidosis; Vasculitis; MS; Myasthenia gravis; Psoriasis; Psoriatic arthritis; Rheumatoid arthritis; Sjögren's; SLE; Crohn's disease; Ulcerative colitis; Antiphospholipid syndrome; Pernicious anemia; Idiopathic thrombocytopenic purpura; Other autoimmune conditions
Other conditions	Serious hemorrhage; Thrombocytopenia; Blood/blood product transfusion; Surgeries/medical procedures; Tissue graft/transplant/artificial valve placement; Other medical conditions
Infections	Cellulitis; Skin abscess; Herpes zoster; Otitis; Sinusitis; Upper respiratory infection; Bronchitis; Pneumonia; Tuberculosis (active); COVID-19; Gastroenteritis; Diverticulitis; Urinary tract infection; Osteomyelitis; Meningitis; Endophthalmitis; Lyme disease (with/without CNS involvement); HIV/AIDS; Hepatitis B (acute/chronic/latent, including reactivation when indicated); Hepatitis C (acute/chronic/latent); Other viral hepatitis; Progressive multifocal leukoencephalopathy (JC virus); Sepsis; Other infections.

Events are considered serious if they result in death, are life-threatening, require a new or prolonged hospitalization, cause a persistent or significant disability, involve a congenital anomaly or birth defect, or are judged by the provider to be medically important. Any event that meets the criteria for a serious event or falls into a TAE category (such as serious infection, malignancy, hepatic events, hypersensitivity or anaphylaxis, cardiovascular events, venous thromboembolism, gastrointestinal perforation, herpes zoster, autoimmune conditions, or COVID-19), requires completion of the TAE form for additional data collection.

All reported TAEs are reviewed by the PPD™ CorEvitas™ Pharmacovigilance team for quality control and case validation against case definitions, including review of the event type, event

term, event date, seriousness, and minimum data elements required to support case validation against available supporting primary source medical records and documentation.

For adverse events and comorbidities that may occur during the period prior to enrollment, chart abstraction is limited to the review of AEs collected at the time of registry enrollment. Site facilitators provide any updates if information available in the medical records differs from what was reported at enrollment. Therefore, typical measures collected, and reviews conducted for adverse events occurring after enrollment (see section 8.7.2), such as information obtained through TAE forms, are not available for pre-enrollment events.

Prespecified AESI will include:

- Severe hypersensitivity reactions including infusion related reactions (IRR) or anaphylaxis
    - IRR: any signs or symptoms experienced on the same day of Inebilizumab administration. Symptoms can include: hypotension, shock, angioedema, respiratory distress (bronchospasm, laryngeal edema), throat irritation, urticaria/hives/rash, persistent abdominal pain, nausea/vomiting, or other.
    - Severe hypersensitivity reactions: severe reactions resulting from unintended and unwanted stimulation of immune or inflammatory cells by inebilizumab. Note that severe hypersensitivity reactions reported or identified on the same day of inebilizumab infusion will be considered as IRR.
    - Anaphylaxis: any IRR or hypersensitivity reactions meeting the Sampson's criteria of anaphylaxis.
    - Note: Timing of infusion-related reaction will not be available for any hypersensitivity events retrieved through chart abstraction. Therefore, IRR and hypersensitivity reactions cannot be identified for the subjects with pre-enrollment inebilizumab initiation.
- All Infections
- Serious infections
- Opportunistic infections (serious and non-serious; including active tuberculosis; per case definitions adapted from guidance by Winthrop et al.) [9]
- Any malignancies

8.3.3 Covariate Assessment

Covariates listed in section 8.3.2.2 will be used to describe the study cohort.

8.3.4 Validity and Reliability

All PPD CorEvitas Registries are subject to standard operating procedures (SOPs) that govern monitoring and, if required, correction to the data. Specifically, the data for each site is reviewed by Clinical Data Management (CDM) or other delegated PPD CorEvitas representative for completeness and internal consistency at regular intervals. CDM generates a list of queries for each site, sends to the clinical site coordinator, and requests verification or correction for each

query within 5 to 7 business days of receipt. CDM or another designated PPD CorEvitas representative enters corrected data onto the PPD CorEvitas database. An audit trail of all corrections to the data, including corrections, author and date, is stored in the PPD CorEvitas database.

8.4 Data Sources

The CorEvitas SPHERES NMOSD Registry is a prospective, multicenter, non-interventional, research study for subjects with NMOSD under the care of a licensed neurologist or qualified physician extender launched in June 2021. Longitudinal follow-up data is collected from both subjects and their treating neurologists during routine clinical encounters using Registry questionnaires. These questionnaires collect data including, but not limited to: patient demographics, disease phenotype, duration, medical history (including all prior and current treatments for NMOSD and other concurrent autoimmune diseases, if applicable), smoking status, alcohol use, disease activity and severity, details about previous and incident relapses, as well as other clinician- and patient-reported outcomes, comorbidities and adverse events, infections, hospitalizations, and other targeted safety outcomes.

Since its launch in June 2021 to June 30, 2025, the Registry has enrolled subjects with NMOSD from 30 private and academic clinical sites with 84 physicians throughout 21 states in the US.

For subjects reporting inebilizumab use prior to CorEvitas SPHERES registry enrollment, subject demographics, lifestyle, treatment history, clinical and disease characteristics will be retrieved directly from medical charts. The clinical visit nearest to the time of inebilizumab initiation will be used.

8.5 Study Size

Registry data as of October 31, 2025 was used for study feasibility. There are a total of 69 subjects diagnosed with NMOSD according to the 2015 IPND consensus diagnostic criteria who are AQP4-IgG+ and initiated inebilizumab prior to, at, or after enrollment into the SPHERES Registry. Of those, 50 (72%) initiated inebilizumab prior to enrollment and 19 (28%) initiated inebilizumab at or after enrollment.

This is a descriptive study with no intent of hypothesis testing; therefore, power analyses were not conducted.

8.6 Data Management

Data quality is controlled, monitored, and managed according to the PPD™ CorEvitas™ Master Registry Monitoring Plan (RMP). All study personnel must complete standardized protocol

training prior to initiating data collection. Each Investigator is also required to designate one staff member as the primary Registry Coordinator responsible for addressing data clarifications requests from PPD CorEvitas in a timely manner. All data collectors in the field have continuous access to a dedicated Registry Manager who answers questions and provides guidance on specific definitions and clinical situations.

Data quality review (i.e., monitoring) occurs at the site level as well as in aggregate to check for Case Report Form (CRF) completeness, consistency, and compliance with all data collection requirements set forth in the registry protocol. Monitoring is performed in addition to the edit checks and event completion rules configured in the 21 CRF Part 11 compliant Electronic Data Capture (EDC) system. The majority of monitoring is conducted using centralized (i.e., remote) methods in accordance with the Agency for Healthcare and Research Quality's (AHRQ) data collection and quality assurance recommendations [10]. These methods include but are not limited to routine remote monitoring visits and automated database quality control listings. Onsite audits of source data are also performed for a subset of registry sites as defined by the Master RMP.

Remote monitoring visits are conducted for the duration of the registry beginning when the first patient is enrolled. Qualified monitors within PPD™ CorEvitas™ Clinical Data Management (CDM) department are responsible for conducting remote monitoring visits. Registry Managers are responsible for site retraining and resolving any compliance issues identified during these visits. Sites also receive data clarification requests (i.e., queries) at regular intervals from designated CDM and Pharmacovigilance personnel. Queries are issued and tracked through the study's EDC system. Sites are required to respond to data queries within 5 to 7 business days of receipt.

8.6.1 Obtaining Data Files

All queries are evaluated, and analyses are performed by experienced biostatisticians and epidemiologists. All queries will be conducted by PPD CorEvitas, and the results will be generated and provided as summary reports to the study sponsor. Review and analysis of the summary reports will be performed by study sponsor. All original data and databases will be stored by PPD CorEvitas according to their SOPs.

8.6.2 Linking Data Files

We will use the de-identified PPD CorEvitas datasets only. No linkage to other datasets will be attempted in this project.

8.6.3 Review and Verification of Data Quality

The analysis will be reviewed by the research team with expertise in the PPD CorEvitas data, causal inference methodologies, and neurology, to ensure validity.

8.7 Data Analysis

8.7.1 Planned Analyses

The following describes the statistical analysis that will be used to evaluate this study's objectives. Alterations to the analysis plan may be recommended by the PPD CorEvitas team after Statistical Analysis Plan (SAP)/protocol approval. These may be intended, but not limited, to enhance clinical interpretation, address departures from statistical assumptions, or ameliorate any unforeseen challenges in the original protocol. Any changes to the methodology recommended by the PPD CorEvitas team will be communicated to the client and incorporated into an amended protocol (if applicable), approved SAP, and noted in the final report.

8.7.1.1 Primary Analysis

8.7.1.1.1 Patient Characteristics at the Index Visit

Patient sociodemographic, lifestyle characteristics, NMOSD disease characteristics, comorbidities, and disease severity measures at index visit (see section 8.2.4 for index visit definition) will be summarized using descriptive summary statistics, including means and standard deviation (SD) for continuous variables, and counts and percentages for categorical variables (Table 1 and Table 2). Table 1 will be stratified by whether inebilizumab initiation was prior to registry enrollment (prevalent subject) or at/after registry enrollment (incident subjects). For prevalent subjects without chart review data, and for measures not collected through chart review, values from the enrollment visit will be used in Table 1. Table 2 will describe disease severity measures (PROs and ClinROs) only on the incident subjects. See Section 8.1.1 for details on variables derived from chart abstraction.

8.7.1.1.2 Persistence of Inebilizumab

Time to inebilizumab discontinuation will be computed as the months from inebilizumab initiation to discontinuation. Subjects with no reported drug stop will be considered to be on inebilizumab treatment and censored at the last date of on-study drug log attestation or, if available, the most recent drug entry recorded on a TAE form or Relapse form. Temporary interruptions of ≤90 days will be permitted, provided no new biologic therapy is initiated during that period.

KM curves of the time from inebilizumab initiation to discontinuation will be produced to estimate inebilizumab persistence (drug survival). KM methods account for varying lengths of exposure

and appropriately handle censoring for subjects who remain on therapy at the time of the data cut.

From the KM curves, the 10th percentile of time to discontinuation (i.e., the time point at which an estimated 10% of subjects are expected to have discontinued inebilizumab, or the time by which 90% of subjects remain on inebilizumab without discontinuation) will be reported. Table 3 will estimate the 5th, 10th, 15th and 20th percentiles of time to discontinuation, along with the corresponding 95% CIs.

The estimated probability of remaining on treatment (i.e., persistence) will be obtained from the KM curve at prespecified 6-month intervals following inebilizumab initiation and presented in Table 4. These estimates represent the probability that a subject remains on inebilizumab and has not discontinued treatment at each timepoint. Corresponding 95% CIs for persistence probability estimates at each time point will be presented. Estimates will be provided up to the time point at which at least 10% of subjects remain at risk.

8.7.1.1.3 Time to First Attack and Annualized Attack Rate

Time to first attack (in months) will be measured from the date of inebilizumab initiation to date of discontinuation. To account for the drug's elimination and potential residual biologic effect (half-life ≈18 days), a 3-month risk extension period following discontinuation will be included in the exposure window. Any attack occurring during this risk extension period will be considered an event. For subjects without a reported discontinuation, exposure time will be censored at the date of the most recent date of on-study drug log attestation or, if available, the most recent drug entry recorded on a TAE form or Relapse form.

If a subject experiences an attack event and does not discontinue treatment after the attack, the exposure time for that subject will be censored for a 30-day period beginning on the date of the attack. Any additional attack events occurring during this 30-day period will be assigned to the initial attack event and not considered a new attack. Exposure time will resume on the 31st day following the attack event date, continuing until the end of the risk extension period (if discontinuation occurs), or to the date of the final on-study drug log attestation date (if no discontinuation is reported) or, if available, the most recent drug entry recorded on a TAE form or Relapse form.

KM curves of the time from inebilizumab initiation to first NMOSD attack will be produced to estimate inebilizumab attack-free probability. From these curves, the 10th percentile of time to first attack (i.e., the time point at which an estimated 10% of subjects are expected to have

experienced first NMOSD attack while on inebilizumab, or the time at which 90% of subjects remain attack-free) will be reported. Table 5 will present estimates of the 5th, 10th, 15th and 20th percentiles of time to first attack, along with the corresponding 95% CIs. If more than 20% of subjects experience an attack by the end of follow-up, the reported percentiles will be increased accordingly.

The estimated probability of remaining attack-free will be obtained from the KM curve at 6-month intervals following inebilizumab initiation and presented in Table 6. These estimates will represent the probability that a subject has not experienced an NMOSD attack at each time point. Corresponding 95% CIs for attack-free probability estimates at each time point will be presented. Estimates will be provided up to the time point at which 10% of subjects remain at risk.

The annualized attack rate (AAR) will be estimated using a negative binomial model based on the total number of NMOSD attacks normalized by the total PY of exposure. The number of NMOSD attacks will be the dependent variable and the logarithm of PY of exposure will be included as an offset term. The offset term accounts for varying durations of follow-up among subjects, allowing the model to estimate an attack rate standardized to one year of exposure. No covariates will be included in the model because this is a descriptive analysis, and no additional adjustment is planned. If the number of observed attacks is too small to support reliable estimation or model convergence, crude AARs will be presented. The crude AAR will be calculated as the total number of attacks divided by the total number of PY of exposure with corresponding 95% CIs computed assuming a Poisson distribution.

The AARs will be calculated overall and by year (Years 1, 2, 3, 4), following inebilizumab initiation and presented in Table 7.

8.7.1.1.4 Incidence of Adverse Events and Adverse Events of Special Interest

Adverse events and AESIs will first be summarized descriptively as the number and proportion of subjects experiencing at least one occurrence of each event category. These event categories will include: at least one adverse event, at least one serious adverse event, most frequent adverse events (events occurring in more than 10% of subjects in the study population), and at least one AESI. Each subject will be counted once per event category.

To account for varying durations of exposure and to characterize the exposure adjusted incidence of subjects experiencing at least one event, EAIRs will be calculated for the same event categories. Time at risk will be defined as the time from inebilizumab start to the onset

date of the first occurrence of the event for subjects experiencing the event, and from inebilizumab start to the end of the exposure period for subjects not experiencing the event. EAIRs will be computed as the number of subjects experiencing at least one occurrence of the event divided by the total person-years at risk and expressed per 100 person-years. Corresponding 95% confidence intervals will be calculated assuming a Poisson distribution for the number of subjects with at least one event, using exact confidence limits.

To account for multiple events within subjects and to characterize the total burden of events over time, event-based incidence rates will also be computed. The event incidence rate (EIR) adjusted by person-years will be estimated using a negative binomial model based on the total number of events (including repeat events within individual subjects) divided by the total PY of exposure. The number of events will be the dependent variable and the logarithm of PY of exposure will be included as an offset term. The offset term accounts for varying durations of exposure among subjects. No covariates will be included in the model because this is a descriptive analysis, and no additional adjustment is planned. If the number of observed events is too small to support reliable estimation or model convergence, an exact Poisson distribution may be used as an alternative.

For all analyses, adverse events (see Table 8.3.2.4) that occur during the exposure period of each individual event type (e.g., pneumonia) or category (e.g., infections) will be included. At the end of study (date of analytic datacut), the total exposure (in person-years) will be computed.

8.7.1.2 General Considerations

N/A

8.7.1.3 Missing or Incomplete Data and Lost to Follow-up

Missing data could be expected for all patient characteristics (e.g., age, etc.); however, the number of subjects with missing data is expected to be small. For every variable, the number of subjects with missing information can be reported.

For prevalent subjects where chart abstraction was not performed due to reasons such as unsuccessful chart review or unavailable medical records, time-to-attack analyses will be conducted among subjects with confirmed chart review, as attacks and attack-free follow-up cannot be reliably ascertained without abstracted chart data.

8.7.1.4 Descriptive Analysis

8.7.1.4.1 Description of Study Enrollment

N/A

8.7.1.4.2 Description of Subject/Patient Characteristics

See above section 8.7.1.1.1

8.7.1.5 Analysis of the Primary, Secondary, and Exploratory Endpoint(s)

See above section 8.7.1.1

8.7.1.6 Sensitivity Analysis

N/A

8.7.1.6.1 Subgroup Analysis

N/A

8.7.1.6.2 Stratified Analysis

Stratified analyses will be conducted only when subgroup sample sizes exceed 10 (n>10), in accordance with Surveillance, Epidemiology and End Results-Medicare Health Outcomes Survey guidelines for masking small cell sizes to protect privacy and avoid unstable estimates [11].

Analyses for Table 1 will be stratified by prevalent and incident subjects.

Prevalent subjects are subjects with inebilizumab initiation prior to the date of registry enrollment.

Incident subjects are subjects with inebilizumab initiation at or after the date of registry enrollment.

Primary Objective 1 and 2 analyses (i.e., shell Tables 3-7 and Figures 1-2) will be stratified by first-line, second-line, and third line+ (and higher) inebilizumab therapy. If sample sizes for individual line of therapy categories do not exceed 10, categories will be collapsed into first-line versus second-line+ (and higher).

First-line inebilizumab therapy is defined as initiation of inebilizumab as the first maintenance treatment for NMOSD, with no prior reported history of rituximab, eculizumab, satralizumab, ocrelizumab, ofatumumab, sarilumab, or tocilizumab. Subjects may have a history of, or prior use of, other biologic or small-molecule therapies for indications unrelated to NMOSD.

Second-line inebilizumab therapy is defined as initiation of inebilizumab following prior use of one NMOSD-directed biologic therapy, including rituximab, eculizumab, satralizumab, ocrelizumab, ofatumumab, sarilumab, or tocilizumab. Subjects must have discontinued or switched from one of these prior biologic therapies before starting inebilizumab.

Third-line or higher inebilizumab therapy is defined as initiation of inebilizumab following prior use of two or more NMOSD-directed biologic therapies, including rituximab, eculizumab, satralizumab, ocrelizumab, ofatumumab, sarilumab, or tocilizumab. Subjects must have discontinued or switched from all previously used NMOSD-directed biologic therapies before starting inebilizumab.

Receipt of the following treatments prior to inebilizumab initiation will not preclude classification as first-line, second-line, or third-line or higher therapy.

- IST (azathioprine, cyclophosphamide, cyclosporine, dimethyl fumarate, diroximel fumarate, fingolimod, leflunomide, cladribine, methotrexate, monomethyl fumarate, mycophenolate mofetil, siponimod, tacrolimus, teriflunomide, mitoxantrone)
- GS (dexamethasone, methylprednisolone, prednisolone, prednisone)
- Immunoglobulin (Ig) therapy
- Other (glatiramer acetate, sulfasalazine, hydroxychloroquine, other)

8.7.1.6.3 Sensitivity Analysis for Residual Confounding and Bias

N/A

8.7.1.6.4 Other Sensitivity Analysis

N/A

8.7.2 Analysis of Safety Endpoint(s)/Outcome(s)

Safety events of interest are ascertained from Provider Follow-up Questionnaires and/or TAE Questionnaires (for adverse events that are serious and/or for registry-defined safety events of

interest). All reported Targeted Events are reviewed by the CorEvitas Pharmacovigilance team for quality control and case validation against case definitions, including review of the event type, event term, event date, seriousness, and minimum data elements required to support case validation against available supporting primary source medical records and documentation. The safety outcomes of interest will be reported for subjects who initiate inebilizumab prior to, at, or after registry enrollment.

Adverse events of special interest will include: severe hypersensitivity reactions including infusion related reactions and anaphylaxis, infections, opportunistic infections (serious and non-serious; including active tuberculosis; per case definitions adapted from guidance by Winthrop et al.) [9], and any malignancies.

Table 9 will present the number and proportion of subjects with:

- at least one adverse event, at least one serious adverse event, death
- at least one adverse event of special interest
- each adverse event of special interest
- most frequent adverse events

Adverse events occurring in more than 10% of subjects in the study sample will be considered most frequent adverse events. Table 9 will list these most frequent adverse events and summarize the number and proportion of subjects experiencing at least one occurrence of each event.

Table 10 will present the EAIR for the event categories in Table 9. Time at risk will be defined as the time from inebilizumab start to the onset date of the first occurrence of the event for subjects experiencing the event, and from inebilizumab start to the end of the exposure time for subjects not experiencing the event. EAIR will be calculated as the number of subjects experiencing at least one occurrence of the event divided by the total person-years at risk and scaled to 100 PY. The corresponding 95% confidence intervals will be computed assuming a Poisson distribution. Each subject will contribute at most one event to the numerator for a given adverse event; multiple occurrences of the same adverse event within a subject will not be counted more than once.

Table 11 will summarize the EIR for adverse events of special interest. The EIR for each AESI will be estimated using a negative binomial model with the total number of events (including multiple occurrences of the same event within subject) as the dependent variable and the

logarithm of person-years of exposure as an offset term. The offset term accounts for varying durations of exposure across subjects. Exposure time will be calculated from the date of inebilizumab start to the date of discontinuation. Subjects with no reported inebilizumab stop date will be considered to be on inebilizumab treatment and censored at the last date of on-study drug log attestation or, if available, the most recent drug entry recorded on a TAE form or Relapse form. Temporary interruptions of ≤90 days will be permitted, provided no new biologic therapy is initiated during that period. Event incidence rates will be expressed per 100 person-years by multiplying the EIR by 100. No covariates will be included in the model, as the analysis is descriptive and no additional adjustment is planned. Each subject may contribute multiple events to the numerator for a given adverse event.

If the number of observed events is too small to support reliable estimation or model convergence, an exact Poisson approach may be used.

8.7.3 Quality Control

PPD CorEvitas or its designee monitors the conduct of the registry at each investigative site. Monitoring is primarily conducted remotely. Onsite monitoring visits are conducted once every three years, as needed, or as requested. A review of registry records including, but not limited to, the informed consent forms, questionnaires, original source documents such as supporting medical records and office notes, subject study files, and any other registry documentation is conducted in accordance with applicable regulatory guidelines and the protocol. PPD CorEvitas and its designees are required to maintain the confidentiality of all subjects during and after an on-site monitoring visit.

Quality control checks are built into the on-screen data entry systems in an attempt to reduce queries and provide immediate feedback to the investigator regarding inadvertent omissions and out of range or noncompliant values. Changes made at any time are recorded in an audit trail that includes the date, time, and electronic ID of the person making the change.

PPD CorEvitas will address and resolve discrepancies by requesting clarifications and/or missing data from the investigator as needed. Each investigator is expected to designate a point of contact to address such inquiries and to promptly address and resolve issues. Representatives or designees from PPD CorEvitas reserve the right to perform random or systematic audits of PPD CorEvitas Questionnaires and PII Forms at an investigator’s site in order to assess the accuracy of the reported data compared to the information contained in the original medical records.

8.8 Limitations of the Research Methods

The CorEvitas SPHERES Registry used in this research includes a sample of adults with NMOSD from private and academic sites that are not necessarily representative of all adults with NMOSD in the US. In particular, these are subjects with clinical visits with neurologists and are willing to participate in a registry. Thus, results from this study may not be generalizable to the broader NMOSD population.

Patient chart data abstraction will be required for the majority of subjects because inebilizumab initiation occurred prior to entry into the CorEvitas SPHERES Registry. It is possible that data collected retrospectively will be inaccurate or have more missingness than among those who initiated at or after enrollment, however, this is necessary to most accurately characterize subjects and identify the patient experience (persistence and attacks), while ensuring a sufficient sample size for meaningful analyses.

Attacks and safety events occurring prior to CorEvitas SPHERES Registry enrollment cannot be verified.

8.8.1 Internal Validity of Study Design

N/A

8.8.1.1 Measurement Error(s)/Misclassification(s)

History of medication use prior to enrollment is derived from what is reported by the neurologist within the registry, rather than prescribing or administration records. Some misclassification of treatment persistence is possible, particularly if documented initiation does not correspond to receipt of infusion. However, discontinuation is expected to be reliably captured, and any misclassification is anticipated to be limited and non-differential. The “cause” of visits is not captured, although the assumption can likely be made that the visit is “NMOSD related.”, and there are no measures of patient adherence.

8.8.1.2 Information Bias

N/A

8.8.1.3 Selection Bias

Selection bias may be introduced if certain subgroups of patients (e.g., healthier or sicker patients) are routinely included or excluded from the registry. This potential bias should not affect the validity but may affect the generalizability of results.

8.8.1.4 Confounding

The current study is purely descriptive and will draw no causal inferences. Therefore, there will be no statistical adjustments for confounding.

8.8.2 External Validity of Study Design

The CorEvitas SPHERES Registry used in this research includes a sample of adults with NMOSD from private and academic sites that are not necessarily representative of all adults with NMOSD in the US. In particular, these are subjects with clinical visits with neurologists and are willing to participate in a registry. Thus, results from this study may not be generalizable to the broader NMOSD population.

8.8.3 Analysis Limitations

Because NMOSD attacks are infrequent and the analyses are descriptive in nature, the number of observed attack events is expected to be low. The limited number of events may reduce the precision of the KM estimates of attack-free probability, particularly at later time points when fewer subjects remain under observation due to censoring. Year-by-year summaries of AARs may also be limited by small numbers of subjects contributing data within each interval, leading to unstable or less precise estimates. In such cases, results will be presented descriptively, with appropriate acknowledgment of the limited information available.

8.8.4 Limitations Due to Missing Data and/or Incomplete Data

As an observational database, the CorEvitas SPHERES Registry does contain records with some missing data, however, the number of subjects (with post-enrollment inebilizumab drug start) with missing data is expected to be small. For the subset of subjects who initiated inebilizumab prior to registry enrollment, missing data might be higher due to retrospective data collection among these subjects and may reduce precision of estimates. We will report statistics overall and by prevalent and incident subjects to help identify variables that may have bias due to missing data.

8.9 Other Aspects

N/A

9. Protection of Human Subjects

This study will comply with all applicable laws, regulations, and guidance regarding human subject protection including data privacy. The data used for this study will not involve interaction or interviews with any subjects and the data does not include any individually identifiable data (e.g., does not include names, addresses, social security or medical record numbers, or other obvious identifiers), and as such is not research involving human subject as defined at 45 CFR 46.102(f)(2).

9.1 Informed Consent

Subjects that entered the registry went through the informed consent process. This retrospective study of registry data will use only existing statistically de-identified data from the registry and investigator(s) will report data in a way that subjects cannot be identified, directly or through identifiers linked to subjects, and as such is both exempt from 45 CFR 46.101(b)(4) and from all 45 CFR part 46 requirements.

9.2 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

Analysis will follow the SAP utilizing data from the IRB-approved PPD CorEvitas SPHERES Registry study and will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Pharmacoepidemiology Practices (GPPs).

9.3 Subject Confidentiality

Reidentification may occur when patient direct identifiers (e.g., name, address, etc.) are linked to the de-identified data. The PPD CorEvitas patient personally identifiable information (“PII”) is accessed, managed, and processed by the third party known as the Honest Broker. The Honest broker is responsible for storing and maintaining CorEvitas Subject PII to ensure its strict separation from clinical and health outcomes data that are also collected for a CorEvitas registry (“Clinical Data”). Thus, the CorEvitas SPHERES NMOSD Registry is fully de-identified prior to analysis with subjects’ direct identifiers (e.g., name, address, etc.) stored separately form clinical data. However, increased computing power and improved mathematical algorithms have raised the risk of reidentification of subjects from publicly available information especially for rare conditions or comorbidities [12]. In the CorEvitas SPHERES NMOSD Registry, the risk of this sort of reidentification is extremely rare because registry data represents relatively small fraction of the total population with the disease. In addition, output using the data is always presented in an aggregated form and never reported on a set of several potentially identifying characteristic for any given subject.

No patient identifiable information will be shared with Amgen. Amgen will only have access to deidentified data from the CorEvitas SPHERES Registry, thereby maintaining subject confidentiality.

10. Collection, Recording, and Reporting of Safety Information and Product Complaints

This study is a secondary analysis of observational data from subjects enrolled in the CorEvitas SPHERES registry. Any safety data identified through the SPHERES Registry will have been

previously collected and reported to Amgen in accordance with local regulations and routine pharmacovigilance practices. For the purposes of this secondary data analysis, the safety outcomes listed in section 8.3.2 will be documented and analyzed. These outcomes will be presented in aggregate in the final study report as incidence rates. See section 8.3.2 for safety outcomes and definitions.

11. Administrative and Legal Obligations

11.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. Amgen and its collaborators reserve the right to terminate the study at any time.

12. Plans for Disseminating and Communicating Study Results

This study will be submitted for publication.

12.1 Publication Policy

All analyses for the public domain are subject to the PPD CorEvitas publication policy (please see the full policy for details; the policy is available upon request). Briefly, the policy describes our adherence to industry best practices for the development, conduct and reporting of research.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.

- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

13. References

[1] D. Wingerchuk, B. Banwell, J. Bennett, P. Cabre, W. Carroll, T. d. S. J. Chitnis, K. Fujihara, B. Greenberg, A. Jacob, S. Jarius, M. Lana-Peixoto, M. Levy, J. Simon, S. Tenembaum, A. Traboulsee, P. Waters, K. Wellik, B. Weinshenker and International, "International consensus diagnostic criteria for neuromyelitis optica spectrum disorders," *Neurology,* vol. 85, no. 2, pp. 177-89, 2015.

[2] K. Holroyd, G. Manzano and M. Levy, "Update on neuromyelitis optica spectrum disorder," *Curr Opin Ophthalmol,* vol. 31, no. 6, pp. 462-468, 2020.

[3] D. Wingerchuk, B. Weinshenker, D. McCormick, S. Barron, L. Simone and L. Jarzylo, "Aligning payer and provider strategies with the latest evidence to optimize clinical outcomes for patients with neuromyelitis optica spectrum disorder," *J Manag Care Spec Pharm,* vol. 28, no. 12-a Suppl, pp. S3-S27, 2022.

[4] T. Nie and H. Blair, "Inebilizumab: A Review in Neuromyelitis Optica Spectrum Disorder," *CNS Drugs,* vol. 36, no. 10, pp. 1133-1141, 2022.

[5] E. Sherman and M. Han, "Acute and Chronic Management of Neuromyelitis Optica Spectrum Disorder," *Curr Treat Options Neurol,* vol. 17, no. 11, p. 48, 2015.

[6] A. Romeo, "Recent advances in the treatment of neuromyelitis optica spectrum disorders," *Curr Opin Rheumatol,* vol. 33, no. 3, pp. 233-239, 2021.

[7] K. Giglhuber and A. Berthele, "Adverse Events in NMOSD Therapy," *Int J Mol Sci,* vol. 23, no. 8, p. 4154, 2022.

[8] R. L. Southwood, V. H. Fleming and G. Huckaby, Concepts in clinical pharmacokinetics (7th ed.), American Society of Health-System Pharmacists, 2018.

[9] K. L. Winthrop, S. A. Novosad, J. W. Baddley, L. Calabrese, T. Chiller, P. Polgreen, F. Bartalesi, M. Lipman, X. Mariette, O. Lortholary, M. E. Weinblatt, M. Sagg and J. Smolen, "Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance," *Annals of the Rheumatic Diseases ,* vol. 74, no. 12, 2015.

[10] (AHRQ), Agency for Healthcare Research and Quality, "Data Collection and Quality Assurance," in *Registries for Evaluating Patient Outcomes: A User's Guide*, 2020.

[11] National Cancer Institute, "Masking Small Cell Sizes Requirement for SEER-MHOS Research Reports and Manuscripts," [Online]. Available: https://healthcaredelivery.cancer.gov/seer-mhos/support/small_cell_sizes.html. [Accessed 3 February 2026].

[12] G. E. Simon, S. M. Shortreed, R. Y. Coley, R. B. Penfold, R. C. Rossom, B. E. Waitzfelder, K. Sanchez and F. L. Lynch, "Assessing and Minimizing Re-identification Risk in Research Data Derived from Health Care Records," *EGEMS (Wash DC),* p. 6, 2019.

14. Appendices

Appendix A. Detailed Definitions of Disease Activity Measures and Patient-reported Outcomes in CorEvitas SPHERES Registry

<table>
<tr><th>Disease Activity Measures (Range)</th><th></th></tr>
<tr><td>Expanded disability status scale (EDSS)
(Range: 0-10)</td><td>The EDSS is a method of quantifying disability based on measures of impairment in 8 functional systems (FS), from 0 (normal neurologic exam) to 10 (death) in increments of 0.5, based on eight Kurtzke Functional Systems plus ambulation status:
Functional systems:
• pyramidal – muscle weakness or difficulty moving limbs
• cerebellar functions – ataxia, loss of balance, coordination or tremor
• brainstem functions – problems with speech, swallowing and nystagmus
• sensory functions – numbness or loss of sensations
• bowel and bladder functions
• visual (optic) function - problems with sight
• cerebral functions - problems with thinking and memory
• other

EDSS Score is based on an examination by a neurologist after considering the 8 functional systems above.
<table>
<tr><th>Score</th><th>Description</th></tr>
<tr><td>0</td><td>Normal neurological exam, no disability in any FS</td></tr>
<tr><td>1.0</td><td>No disability, minimal signs in one FS</td></tr>
<tr><td>1.5</td><td>No disability, minimal signs in more than one FS</td></tr>
<tr><td>2.0</td><td>Minimal disability in one FS</td></tr>
<tr><td>2.5</td><td>Mild disability in one FS or minimal disability in two FS</td></tr>
<tr><td>3.0</td><td>Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking</td></tr>
<tr><td>3.5</td><td>Moderate disability in one FS and more than minimal disability in several others. No impairment to walking</td></tr>
<tr><td>4.0</td><td>Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m</td></tr>
<tr><td>4.5</td><td>Significant disability but 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. Able to walk without aid or rest for 300m</td></tr>
<tr><td>5.0</td><td>Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m</td></tr>
<tr><td>5.5</td><td>Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m</td></tr>
<tr><td>6.0</td><td>Requires a walking aid – cane, crutch, etc. – to walk about 100m with or without resting</td></tr>
<tr><td>6.5</td><td>Requires two walking aids – pair of canes, crutches, etc. – to walk about 20m without resting</td></tr>
<tr><td>7.0</td><td>Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td><table>
<tr><td></td><td>standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day</td></tr>
<tr><td>7.5</td><td>Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorized wheelchair</td></tr>
<tr><td>8.0</td><td>Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms</td></tr>
<tr><td>8.5</td><td>Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions</td></tr>
<tr><td>9.0</td><td>Confined to bed. Can still communicate and eat</td></tr>
<tr><td>9.5</td><td>Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow</td></tr>
<tr><td>10.0</td><td>Death due to NMOSD</td></tr>
</table></td></tr>
<tr><td>Patient-Reported Outcomes Measures (Range)</td><td></td></tr>
<tr><td>Modified Fatigue Impact Scale (MFIS)
(Range: 0-84)</td><td>The MFIS is a modified form of the Fatigue Impact Scale, based on items derived from interviews with multiple sclerosis patients concerning how fatigue impacts their lives.

MFIS Score is the sum of the scores for the 21 items. Individual subscale scores can also be computed: physical, cognitive, and psychosocial functioning.

Higher scores indicate a greater impact of fatigue on a person's activities.</td></tr>
<tr><td>PainDETECT Questionnaire (PD-Q)
(Range: 0-38)</td><td>Measures 7 aspects of the quality of pain experienced, the chronological pattern (time course), and whether or not the pain radiates.
PD-Q score is the total of three components:
Sum score of the 7 pain items (range: 0-35)
Picture score (+1 if pain attacks with or without pain between them; -1 if persistent pain with pain attacks)
Radiating pain (+2 if yes)

Categories: PD-Q, presence of a neuropathic pain component
Negative (0-12)
Unclear (13-18)
Positive (19-38)</td></tr>
<tr><td>Short-form McGill Pain Questionnaire 2 (SF-MPQ-2)
(Range: 0-10)</td><td>Measures the quality as well as the intensity of both neuropathic and non-neuropathic pain.

Total pain score is the mean of continuous, intermittent, neuropathic, and affective subscores

Subscores take the mean of the following items:
• Continuous subscore: throbbing, cramping, gnawing, aching, heavy, tender
• Intermittent subscore: shooting, stabbing, sharp, splitting, electric shock, piercing
• Neuropathic subscore: hot burning, cold, light touch, itching, tingling, numbness
• Affective subscore: tiring, sickening, fearful, punishing</td></tr>
</table>

	Higher score is more pain
Pain Severity Numeric Rating Scale (Pain Severity NRS) (Range: 0-10)	NRS where 0=no pain and 10=worst imaginable pain
EuroQoL 5-Dimension 5-Level (EQ-5D-5L) (Range for US score: -0.573 to 1)	The 5-level EQ-5D version (EQ-5D-5L) is a self-assessed, health related, quality of life questionnaire. The scale measures quality of life on a 5-component scale: • Mobility • Self-care • Usual activity • Pain/discomfort • Anxiety/depression The EQ-5D-5L score is calculated by first constructing the health state profile using the self-reported level of perceived problems today across the five components (mobility, selfcare, usual activities, pain/discomfort, anxiety/depression), each rated on a scale from 1 (“no problems”) to 5 (“extreme pain or discomfort / unable”). The 5 numbers are then concatenated (e.g., “21354”) and converted into a country specific index score by summing preestimated parameter decrements and subtracting that total from 1, with analogous procedures applied using other national value sets. Scores closer to 1 indicate fewer problems
EQ Health Status VAS (Range: 0 to 100)	Records the patient's self-rated health on a vertical visual analog scale Question: How good or bad is your health TODAY? 0 = the worst health you can imagine 100 = the best health you can imagine
Patient Health Questionnaire 2 (PHQ-2) (Range: 0-6)	Measures the frequency of depressed mood and anhedonia over the past two weeks. The PHQ-2 includes the first two items of the PHQ-9. Questions: Over the past 2 weeks, how often have you been bothered by any of the following problems? 1. Little interest or pleasure in doing things 2. Feeling down, depressed, or hopeless 0 = Not at all; 1 = Several days; 2 = More than half the days; 3 = Nearly every day The PHQ total score is the sum of the 2 items above Categories: • Positive (≥ 3) • If the score is 3 or greater, major depressive disorder is likely.
NMOSD – Disability Index (Range: 0-6)	A novel disability index created with the Guthy Jackson Charitable Foundation (GJCF) and PPD CorEvitas.

	Measures level of disability in 3 domains: • Vision: Visual acuity based on best corrected eye (corrective lenses, pinhole, or refraction). • Mobility: items reflecting wheelchair or equivalent assume impaired ability to transfer, ambulate, or both. • Self-care ability: score derives from a cumulative 3-point score (no assistance required, some assistance required, unable to do alone) for each activity of daily life assessed as follows: attend school/work or perform routine housework; bathing/showering; bowel/bladder management; personal grooming; dressing; food preparation; eating. GJCF NMOSD Disability index score is the mean of the mobility, vision and self-care disability domain scores. Categories: • 0=Full Ability • 1=Extensive Ability • 2=Adequate Ability • 3=Limiting Disability • 4=Moderate Disability • 5=Extensive Disability • 6=Full Disability
Visual Function Questionnaire: Utility Index (VFQ-UI) (Range: 0-1)	Measures visual function health states based off 6 items in the National Eye Institute (NEI) Visual Function Questionnaire-25 (VFQ-25), representing near vision, distance vision, social functioning, role limitations, dependency, and mental health The VFQUI score is calculated first by creating the combined item responses into a 6-digit health state code (e.g., “111111” = best, “555555” = worst). These health states are converted to a preference-based utility index that ranges from 1 (perfect vision health) down to 0 (worst vision health).

Appendix B. Table Shells

Table 1. Patient Demographics and Disease Characteristics at the index visit among NMOSD subjects treated with inebilizumab in the CorEvitas SPHERES Registry, overall and by prevalent and incident use

Characteristic	**Overall N=**	**Prevalent inebilizumab subjects N=**	**Incident inebilizumab subjects N=**
Age at visit			
N			
Mean (SD)			
Median (Q1, Q3)			
Sex			
Male			
Female			
Race			
White			
Black/African American			
Asian			
Other			
Ethnicity			
Hispanic			
Non-Hispanic			
Body Weight (lbs.)			
N			
Mean (SD)			
Median (Q1, Q3)			
Body mass index (BMI)			
Normal/underweight (<25)			
Overweight (25 to <30)			
Obese ≥ 30			
Education			
Less than high school			
High school graduate, diploma, or equivalent			
Some college/Associate's/Trade			
College graduate or higher			
Type of health insurance plan			

Characteristic	**Overall N=**	**Prevalent inebilizumab subjects N=**	**Incident inebilizumab subjects N=**
Private			
Medicare			
Medicaid			
Military/VA			
History of Comorbidities			
Autoimmune Condition[1]			
Cancer/Malignancy Event[2]			
Cardiovascular/Circulatory Event[3]			
Gastrointestinal[4]			
Hepatic Event or Condition[5]			
Metabolic Condition[6]			
Neurologic Event or Condition[7]			
Anxiety			
Depression			
Respiratory Condition[8]			
History of serious infections[9]			
Disease Characteristics			
Newly diagnosed (within 1 year)			
Time since symptom onset (years)			
N			
Mean (SD)			
Median (Q1, Q3)			
Time since diagnosis (years)			
N			
Mean (SD)			
Median (Q1, Q3)			
Diagnosed with NMOSD at the time of their first neurological episode			
Phenotype of first neurological episode			
Optic neuritis			
Acute myelitis			
Area postrema syndrome			
Acute brainstem syndrome			

Characteristic	**Overall N=**	**Prevalent inebilizumab subjects N=**	**Incident inebilizumab subjects N=**
Symptomatic narcolepsy or acute diencephalic syndrome			
Symptomatic cerebral syndrome			
Number of previous attacks (including the initial episode) prior to index visit			
N			
Mean (SD)			
Median (Q1, Q3)			
Number of previous attacks (including the initial episode) prior to index visit			
1			
2			
3+			
Manifestations of previous attacks (including the initial episode) prior to index visit			
Optic neuritis			
Acute myelitis			
Area postrema syndrome			
Acute brainstem syndrome			
Symptomatic narcolepsy or acute diencephalic syndrome			
Symptomatic cerebral syndrome			
Medications for NMOSD			
Previous therapies[10]			
Rituximab			
Approved for NMOSD biologic[11]			
Not approved for NMOSD biologic[12]			
Immunosuppressant therapy (IST)[13]			
Glucocorticoids[14]			
Immunoglobulin therapy (IVIG)			
Other[15]			
Concomitant Therapy[16]			
Immunosuppressant therapy (IST)[13]			
Glucocorticoids[14]			

Characteristic	Overall N=	Prevalent inebilizumab subjects N=	Incident inebilizumab subjects N=
Other[15]			

[1] Autoimmune Event or Condition include Autoimmune thyroid disease/Hashimoto's disease, Sarcoidosis, Vasculitis, Multiple sclerosis, Myasthenia gravis, Psoriasis, Psoriatic arthritis, Rheumatoid arthritis, Sjögren's syndrome, Systemic lupus erythematosus, Crohn's disease, Ulcerative colitis, Antiphospholipid syndrome, Pernicious anemia, Idiopathic thrombocytopenic purpura (ITP), Diabetes mellitus Type 1, Other autoimmune condition.
[2] Cancer/Malignancy Events include Breast cancer, Lung cancer, Colon cancer, Uterine cancer, Cervical cancer, Prostate cancer, Leukemia, Lymphoma, Non-melanoma skin cancer (basal cell), Non-melanoma skin cancer (squamous cell), Melanoma skin cancer, Multiple myeloma, Pre-malignancy, Paraneoplastic syndrome, Other cancer.
[3] Cardiovascular/Circulator Event include Coronary artery bypass graft, Coronary angioplasty w/wo cardiac stent, Cardiac arrhythmia non-serious, Myocardial infarction, Unstable angina, Coronary artery disease non-serious, Congestive heart failure (non-serious), Congestive heart failure (serious), Stroke, Transient ischemic attack, Other cardiac condition (serious), Other cardiac condition (non-serious), Deep vein thrombosis, Pulmonary embolism, Other venous thromboembolism, Other vascular condition (serious), Other vascular condition (non-serious).
[4] Gastrointestinal Events include Gastroesophageal Reflux Disease (GERD)/acid reflux, Gastrointestinal perforation, Other gastrointestinal disorder(non-serious).
[5] Hepatic Event or Conditions include Fatty liver disease/NASH, Hepatic event (requiring biopsy or serious), Hepatic event (increased LFT's >3x ULN), Drug induced liver injury (serious), Other hepatic event (non-serious).
[6] Metabolic Condition includes Hypertension, hyperlipidemia, diabetes mellitus Type 1 and 2, osteoporosis, other metabolic condition.
[7] Neurologic Event or Condition includes Seizure(s), Progressive Multifocal Leukoencephalopathy, Multiple sclerosis, Other neurological disorder.
[8] Respiratory Condition include Asthma, Chronic obstructive pulmonary disease (COPD), Interstitial lung disease/pulmonary fibrosis, Other respiratory condition.
[9] Serious Infections include Cellulitis, Herpes zoster, Otitis, Sinusitis, Upper respiratory infection, Bronchitis, Tuberculosis (active), Pneumonia, COVID-19, Gastroenteritis, Diverticulitis, Urinary tract infection, Osteomyelitis, Meningitis / encephalitis, Endophthalmitis, Lyme disease, HIV/AIDS, Hepatitis B, Hepatitis C, Other viral hepatitis, Progressive Multifocal Leukoencephalopathy, Sepsis, Other infection.
[10] Previous therapy includes treatment started before inebilizumab initiation date.
[11] Eculizumab, satralizumab, ravulizumab
[12] Ocrelizumab, ofatumumab, sarilumab, tocilizumab
[13] Immunosuppressant Therapy includes: azathioprine, cyclophosphamide, cyclosporine, dimethyl fumarate, diroximel fumarate, fingolimod, leflunomide, cladribine, methotrexate, monomethyl fumarate, mycophenolate mofetil, siponimod, tacrolimus, teriflunomide, mitoxantrone.
[14] Glucocorticoids include: dexamethasone, methylprednisolone, prednisolone, prednisone.
[15] Other includes: glatiramer acetate, sulfasalazine, hydroxychloroquine, other.
[16] Concomitant therapy includes treatment in use and newly started/prescribed at inebilizumab initiation date.

Table 2. Patient-Reported Outcomes and Clinician Reported outcomes at the index visit among NMOSD subjects with incident inebilizumab use in the CorEvitas SPHERES Registry

Disease Measure	**Incident inebilizumab subjects N=**
MFIS, Total Score (Range: 0-84)	
N	
Mean (SD)	
Median (Q1, Q3)	
PD-Q (Range: 0-38)	
N	
Mean (SD)	
Median (Q1, Q3)	
PD-Q, presence of a neuropathic pain component	
Negative (0-12)	
Unclear (13-18)	
Positive (19-38)	
EQ VAS (Range: 0-100)	
N	
Mean (SD)	
Median (Q1, Q3)	
VFQ-UI Utility Score (Range: 0-1)	
N	
Mean (SD)	
Median (Q1, Q3)	
EQ-5D-5L, Index Score (Range: -0.57-1)	
N	
Mean (SD)	
Median (Q1, Q3)	
SF-MPQ-2, Total Score (Range: 0-10)	
N	
Mean (SD)	
Median (Q1, Q3)	
Pain severity NRS (Range: 0-10)	
N	
Mean (SD)	

Disease Measure	**Incident inebilizumab subjects N=**
Median (Q1, Q3)	
PHQ-2 (Range: 0-6)	
N	
Mean (SD)	
Median (Q1, Q3)	
PHQ-2, categorical	
Positive (≥ 3)	
EDSS Step Score (Range: 0-10)	
N	
Mean (SD)	
Median (Q1, Q3)	

Figure 1. Kaplan-Meier curve showing the time from inebilizumab initiation to discontinuation among NMOSD subjects in the CorEvitas SPHERES Registry

Figure 2. Kaplan-Meier curve showing the time from inebilizumab initiation to first attack among NMOSD subjects in the CorEvitas SPHERES Registry

Note: Figure 1 and 2 will be stratified by line of therapy.

Table 3. Kaplan-Meier percentile estimates of time to Inebilizumab discontinuation, overall and by line of therapy

	Overall Estimate (95% CI)	**First-line Estimate (95% CI)**	**Second-line Estimate (95% CI)**	**Third-line+ Estimate (95% CI)**
5th percentile				
10th percentile				
15th percentile				
20th percentile				

Table 4. Kaplan-Meier estimates of persistence probability on inebilizumab at 6-month intervals, overall and by line of therapy

	Overall Estimate (95% CI)	**First-line Estimate (95% CI)**	**Second-line Estimate (95% CI)**	**Third-line+ Estimate (95% CI)**
6-month				
12-month				
18-month				
24-month				
30-month				
36-month				
…				

Note: Kaplan-Meier estimates will be displayed at 6-month intervals following inebilizumab initiation, up to the last timepoint at which at least 10% of subjects remain at risk

Table 5. Kaplan-Meier percentile estimates of time to first attack, overall and by line of therapy

	Overall Estimate (95% CI)	**First-line Estimate (95% CI)**	**Second-line Estimate (95% CI)**	**Third-line+ Estimate (95% CI)**
5th percentile				
10th percentile				
15th percentile				
20th percentile				

Table 6. Kaplan-Meier estimates of attack-free probability on inebilizumab at 6-month intervals, overall and by line of therapy

	Overall Estimate (95% CI)	First-line Estimate (95% CI)	Second-line Estimate (95% CI)	Third-line+ Estimate (95% CI)
6-month				
12-month				
18-month				
24-month				
30-month				
36-month				
…				

Note: Kaplan-Meier estimates will be displayed at 6-month intervals following inebilizumab initiation, up to the last timepoint at which at least 10% of subjects remain at risk.

Table 7. Annualized attack rate among NMOSD subjects treated with inebilizumab in the CorEvitas SPHERES Registry

Time on inebilizumab	Subjects with attacks (n, %)	Number of Attacks	Person-Years of exposure	AAR (95% CI)
Overall				
Year 1				
Year 2				
Year 3				
Year 4				

AAR = Annualized Attack Rate, CI = confidence interval, PY = person-years
AAR estimated using a negative binomial regression model with log(PY) as an offset term (no covariates included). 95% CIs use model-based standard errors.

Table 7a. Annualized attack rate among NMOSD subjects treated with first-line inebilizumab in the CorEvitas SPHERES Registry

Table 7b. Annualized attack rate among NMOSD subjects treated with second-line inebilizumab in the CorEvitas SPHERES Registry

Table 7c. Annualized attack rate among NMOSD subjects treated with third-line or higher inebilizumab in the CorEvitas SPHERES Registry

CCI

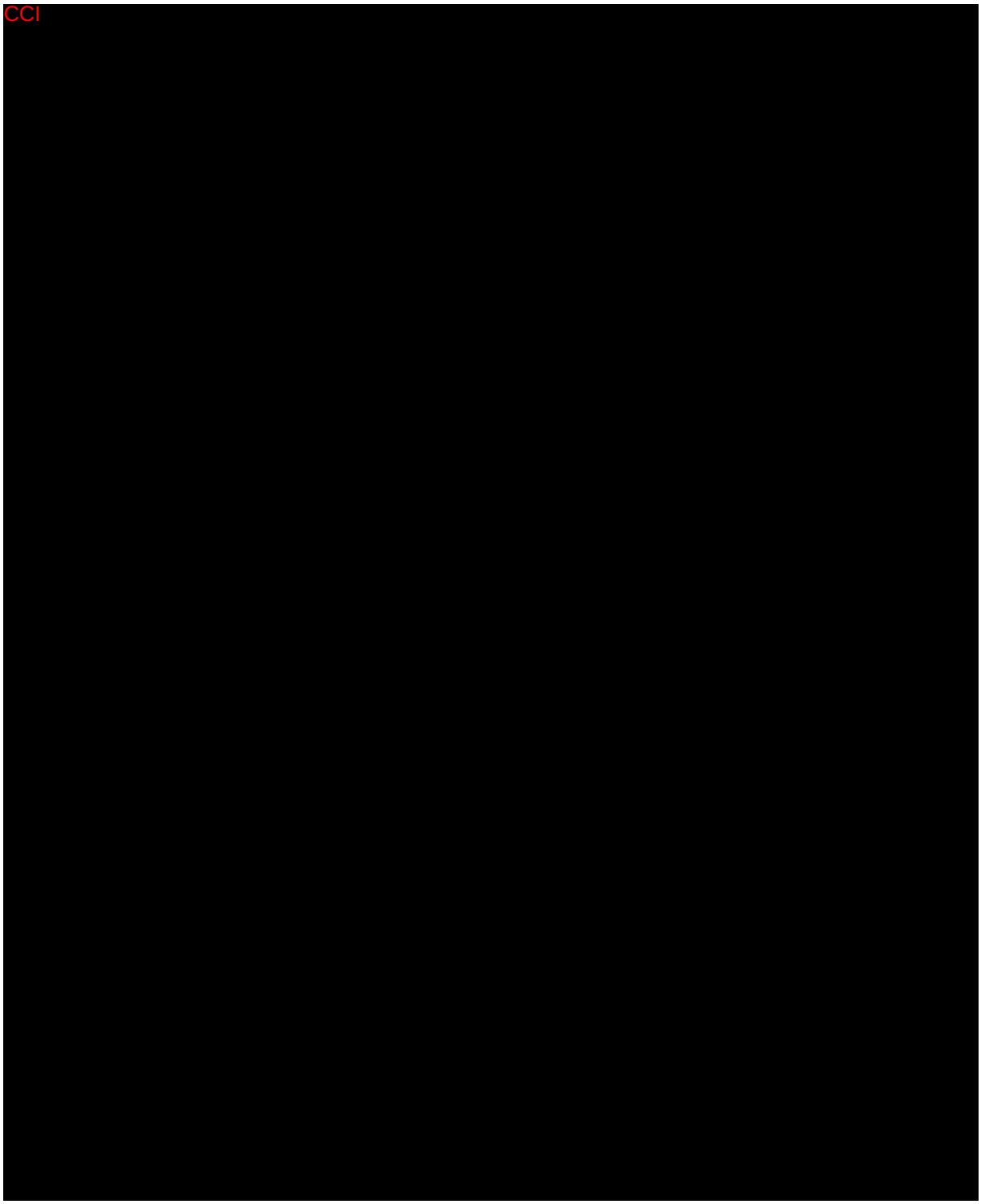


Table 9. Number (%) of NMOSD subjects with adverse events and adverse events of special interest while treated with inebilizumab during the exposure period in the CorEvitas SPHERES Registry

	Subjects, n (%) (N=xx)
Adverse event	
At least one adverse event	
At least one serious adverse event[1]	
Death	
Most frequent adverse events[2]	
[adverse event #1]	
[adverse event #2]	
…	
Adverse event of special interest	
At least one AESI	
Severe infusion-related reaction[3]	
Severe hypersensitivity reaction[3]	
Anaphylaxis	
All infections	
Serious infections	
Opportunistic infections[4]	
Any malignancies	

[1] Events are considered serious if they result in death, are life-threatening, require a new or prolonged hospitalization, cause a persistent or significant disability, involve a congenital anomaly or birth defect, or are judged by the provider to be medically important.
[2] Adverse events that occurred in >10% of subjects in the study population.
[3] Not available for subjects with pre-enrollment inebilizumab start.
[4] Serious and non-serious; including active tuberculosis.

Table 10. Exposure Adjusted Incidence Rate of NMOSD subjects with adverse events and adverse events of special interest while treated with inebilizumab during the exposure period in the CorEvitas SPHERES Registry

	Exposure Adjusted Incidence Rate (95% CI)
Adverse event	
At least one adverse event	
At least one serious adverse event[1]	
Death	
Most frequent adverse events[2]	
[adverse event #1]	
[adverse event #2]	
…	
Adverse event of special interest	
At least one AESI	
Severe infusion-related reaction[3]	
Severe hypersensitivity reaction[3]	
Anaphylaxis	
All infections	
Serious infections	
Opportunistic infections[4]	
Any malignancies	

[1] Events are considered serious if they result in death, are life-threatening, require a new or prolonged hospitalization, cause a persistent or significant disability, involve a congenital anomaly or birth defect, or are judged by the provider to be medically important.
[2] Adverse events that occurred in >10% of subjects in the study population.
[3] Not available for subjects with pre-enrollment inebilizumab start.
[4] Serious and non-serious; including active tuberculosis.

Table 11. Event incidence rate of adverse events of special interest among NMOSD subjects treated with inebilizumab during the exposure period in the CorEvitas SPHERES Registry

Adverse event of special interest	**Event Incidence rate (95% CI)**
Total person-years	
Severe infusion-related reaction[1]	
Severe hypersensitivity reaction[1]	
Anaphylaxis	
All infections	
Serious infections	
Opportunistic infections[2]	
Any malignancies	

[1] Not available for subjects with pre-enrollment inebilizumab start.
[2] Serious and non-serious; including active tuberculosis.

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