TITLE PAGE

Protocol Title: Long-Term, Observational, Registry of Patients With Generalized Myasthenia Gravis Who Have Received Treatment With Complement C5 Inhibition Therapies

Protocol Number: ECU-MG-501

Amendment Number: Not applicable

Compound Number: Soliris® (eculizumab)

Short Title: Registry of Patients With Generalized Myasthenia Gravis Treated With C5 Inhibition Therapies

Sponsor Name: Alexion Pharmaceuticals, Inc.

Legal Registered Address:

121 Seaport Blvd Boston, MA 02210

Regulatory Agency Identifying Number(s):

IND 101,219

Approval Date: 10 July 2019

Sponsor Signatory:

Registry Protocol Title: Long-Term, Observational, Registry of Patients With Generalized Myasthenia Gravis Who Have Received Treatment With Complement C5 Inhibition Therapies

Protocol Number: ECU-MG-501

_____ 7/16/2019

Date

PHYSICIAN'S AGREEMENT

I have read and understand all clinical and administrative sections of the protocol. I agree to participate and conduct the Registry as outlined in the protocol entitled: "Long-Term, Observational, Registry of Patients With Generalized Myasthenia Gravis Who Have Received Treatment With Complement C5 Inhibition Therapies" and in accordance with the guidelines and all applicable government regulations. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Physician

_____

Signature of Physician

_____

Date

ALEXION GMG REGISTRY CONTACTS

Table 1: Contact Information

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Email	Clinicaltrials@alexion.com

Country-specific contact information will be distributed to each participating site.

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: Long-Term, Observational, Registry of Patients With Generalized Myasthenia Gravis Who Have Received Treatment With Complement C5 Inhibition Therapy

Short Title: Registry of Patients With Generalized Myasthenia Gravis Treated With C5 Inhibition Therapy

Rationale:

Complement component 5 (C5) inhibition therapies have been available for patients with generalized myasthenia gravis (gMG) in the United States since the introduction of Soliris® in late 2017. Alexion is developing potential new therapies that leverage a similar mechanism of action are currently being tested in randomized controlled clinical trials.

A need exists for the collection of real-world data on effectiveness, safety, and patterns of drug utilization for these drugs in the indicated population to complement the body of scientific evidence and better inform current and future clinical practice. Currently, there is no data source that collects adequate data on patients with gMG treated with C5 inhibition therapy (C5IT) in the standard clinical practice setting in the US.

Throughout this document, C5IT refers to Soliris and any other C5IT marketed by Alexion. Data will be collected on effectiveness, burden of disease, quality of life, comorbidities, and concomitant medication use to provide evidence on the real-world impact of C5 therapies on gMG-affected patients. Data from this Registry will provide evidence of any sustained clinical and quality of life (QoL) impacts of C5IT in the real-world setting. The Registry is also designed to collect information on real-world treatment patterns (such as drug discontinuation/dose reduction and drug holiday) of C5IT and their impact on patients' status (ie, clinical outcomes, QoL, healthcare resource utilization).

Data will also continue to be collected after C5IT discontinuation or interruption through the end of the study period in patients who remain enrolled in the Registry to provide information on clinical outcomes, QoL, and burden of disease post-discontinuation of C5IT, and capture reasons for discontinuations, interruptions, and restarts. The effects of C5IT use and changes in concomitant medications on patient's outcomes will be described and the results of these analyses will be helpful to inform the medical community on the best treatment patterns for improved clinical outcomes.

The medical community requires additional information on the long-term safety in terms of vaccination factors and pregnancies in this patient population. The Alexion gMG Registry will actively collect long-term clinical outcomes related to the treatment of gMG with C5IT, pregnancies and pregnancy outcomes, and immunization details to characterize the long-term effectiveness and safety profile.

Objectives and Outcomes

The purpose of the Registry is to collect data to address several research objectives including:

Objectives	Outcomes
• To describe the long-term clinical effectiveness and QoL benefit of C5IT – To collect long-term clinical outcome to supplement the clinical trial data – To collect patient-reported outcomes (PROs) in accordance with clinical practice • To describe the impact of changes in C5 therapy (ie, discontinuation or switching or dose reduction) – To capture C5 therapies, patterns of patient care, including the usage of C5Its, patient characteristics, and reasons as well as clinical outcomes associated with medication changes – To collect clinical data on the patterns of drug-response • To describe the long-term benefit-risk ratio – To collect pregnancy data and vaccination outcomes over a long term observation period along with the effectiveness data to describe the benefit-risk over time • To describe patterns of use of concomitant therapy, rate and length of hospitalizations and hospital related resource utilization – To collect concomitant medication-use patterns (eg, changes in use patterns of steroid and immunosuppressant therapy) – To collect admission/discharge date, hospital setting, hospital ward/emergency room (ER), and other hospitalization-related data	**Clinical Outcomes** • Myasthenia Gravis Foundation of America (MGFA) class • MGFA Post Intervention Status (PIS) • Myasthenia Gravis Composite (MGC) • Manual Muscle Testing (MMT) • Physician-reported gMG exacerbations and crises • Serious adverse events (SAEs), including Neisseria infections • Pregnancy and neonatal outcomes **Patient-Reported Outcomes** • Myasthenia Gravis Activities of Daily Living (MG-ADL) Score • Myasthenia Gravis Quality of Life 15-revised (MG QoL15-r) Score • Employment Status (part time/ full time/ unemployed, disabled, retired) **Resource Use** • gMG-related hospitalizations (gMG-related ER visits and overnight hospitalizations [admission diagnosis, date of admission/ discharge, intensive care unit (ICU) visits and discharge setting]) **Therapies** • All C5IT dosing information (changes in dose; dose frequency, dose interruptions, discontinuations, restarts, reasons for discontinuation) • Targeted concomitant medications

Overall Design:

This is a long-term, multicenter, observational, registry of patients with gMG who are treated with C5IT prior to enrollment.

Investigators and physicians will perform the study in full accordance with the Food and Drug Administration (FDA)-approved drug's indication and according to current clinical practice in their center with currently available treatment resources, patient-reported outcome (PRO) instruments, and information and in accordance with the regulations and guidelines governing medical practice and ethics in the US.

At the time of enrollment in the Registry, patient records will be queried for retrospective information about the patients' medical history and gMG disease treatment history. Three of the outcome measures selected based on feasibility and ability to assess effectiveness of C5IT (MGFA class [worst class to date], MG-ADL Score, and MGC) within 6 months prior to the first infusion of C5IT will be required for all patients (Section 4.1). Following enrollment, prospective data collection will be performed using data obtained as part of the routine clinical care and through PRO methods in use, as indicated in the Schedule of Data Collection and

Registry Schematic (Section 1.2 and Section 1.3). Data will be collected using an electronic data capture (EDC) system. The duration of data collection for the Registry will be up to 5 years from the first patient is enrolled.

If an enrolled patient discontinues treatment with C5IT, this will not affect continued enrollment in the Registry. With patient consent, data should be collected for this patient through the end of the registry period, if possible, in order to document clinical characteristics and patient outcomes post-C5IT discontinuation, change to other therapies, and/or therapy interruption.

Number of Patients:

Up to 500 patients with gMG who are receiving treatment with C5IT will be enrolled in order to have adequate representation of the real-world experience of patients with gMG.

Invitations to participate in the Registry will be limited to physicians with ≥ 3 patients with gMG who are receiving treatment with C5IT at time of registry enrollment.

Statistical Analyses:

Prior to the conduct of data analyses, details of planned analyses and patient cohorts will be prespecified in an Epidemiological and Statistical Analysis Plan (ESAP).

Categorical variables will be described using frequencies and percentages and may be modeled using logistic regression, while continuous variables will be described using means, standard deviations, medians, and/or inter-quartile ranges where appropriate, and modeling may be accomplished through generalized linear models, or other statistical techniques where appropriate. When pre-C5IT baseline data is available, evaluation of effectiveness will come from analysis of within-patient changes over time from Baseline.

Registry results will be summarized and reviewed at appropriate intervals based on patient enrollment and scientific considerations.

The ESAPs will describe in detail the methods and variables used in analyses, including those pertaining to truncated and missing data. The extent of missing or truncated data within the analysis datasets will be described in registry reports.

1.2. Schedule of Data Collection

Data Collection	Enrollment[a]	Follow-up[b]
Informed consent	X	
Patient selection	X	
Demographics	X	
Targeted illnesses/ comorbidities[c]	X	
gMG-targeted disease history[d]	X	
Thymoma/ thymectomy history	X	X
Work status (part time/ full time/ disability status)	X	X
Targeted therapies[c]	X	X
C5IT dosing information[e]	X	X
Meningococcal vaccine(s)[f]	X	X
Pregnancy history, breastfeeding, and neonatal outcomes	X	X
Physician-reported gMG exacerbations and crises	X	X
MG-related hospitalizations and ER visits	X	X
MGFA Class	X	X
MGFA PIS	X	X
MG-ADL	X	X
MG-QoL-15-r	X	X
MGC	X	X
MMT	X	X

Note: In the event a patient discontinues C5IT, attempts should be made to continue data collection through the end of study.

[a] Includes retrospective data collection

[b] Includes end of study

[c] See Section 9.2 for examples

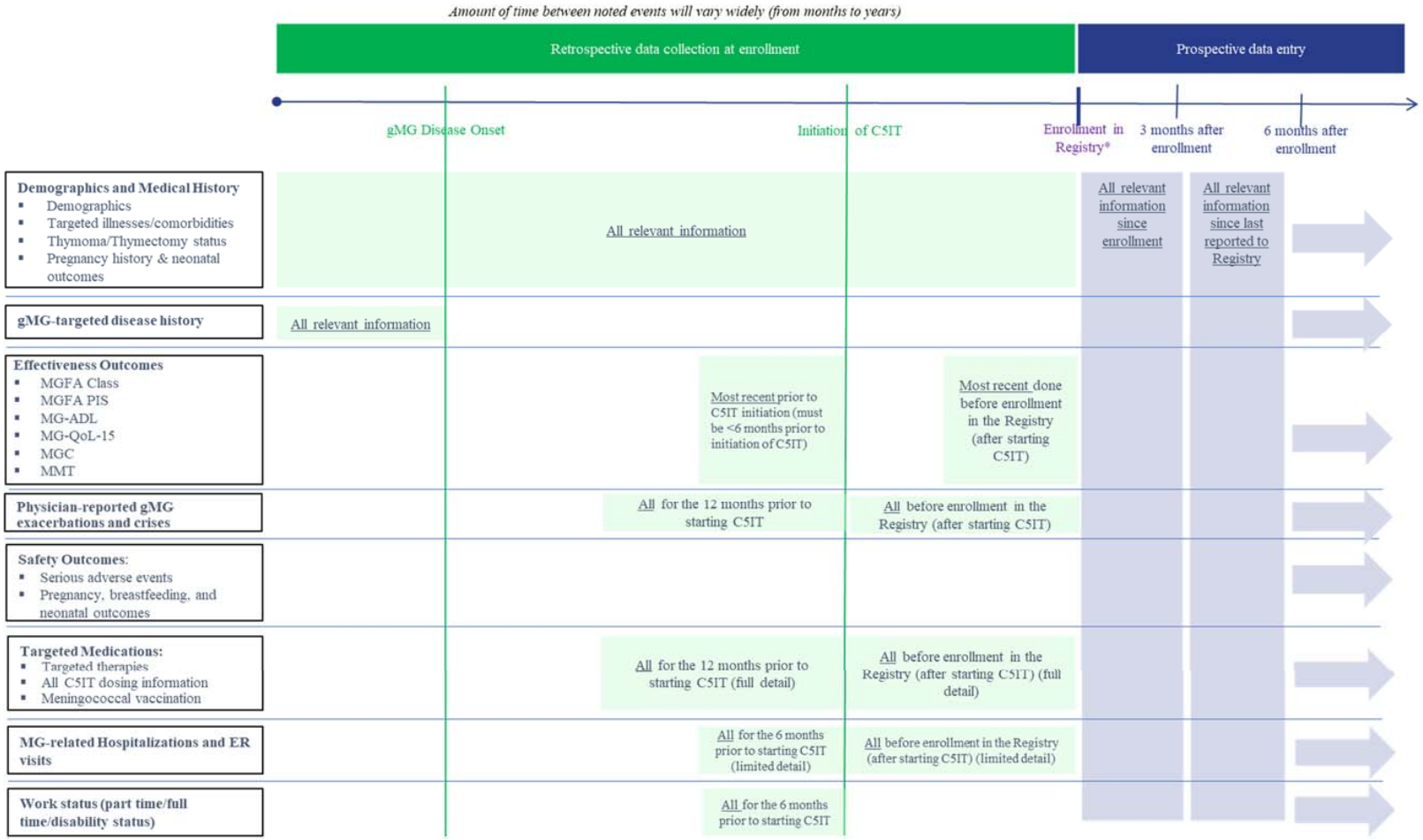
[d] Includes anti-AChR antibody status, disease onset and diagnosis, worst MGFA classification to date

[e] Including start/stop dates, changes, and reasons for discontinuation

[f] Includes vaccination type and timing, including any re-vaccination during follow-up

Abbreviations: AChR = acetylcholine receptor; C5 = complement component 5; C5IT = C5 inhibition therapy; ER = emergency room; gMG = generalized myasthenia gravis; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGC = Myasthenia Gravis Composite; MGFA = Myasthenia Gravis Foundation of America; MG-QoL-15 = Myasthenia Gravis Quality of Life survey (15-item); MMT = Manual Muscle Testing; PIS = Post Intervention Status.

1.3. Registry Schematic



* Patients may be enrolled at any time after starting C5IT

Abbreviations: C5 = complement component 5; ER = emergency room; gMG = generalized myasthenia gravis; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGC = Myasthenia Gravis Composite; MGFA = Myasthenia Gravis Foundation of America; MG-QoL-15 = Myasthenia Gravis Quality of Life survey (15-item); MMT = Manual Muscle Testing; PIS = Post Intervention Status.

2. INTRODUCTION

2.1. Registry Rationale

Complement component 5 (C5) inhibition therapies have been available for patients with generalized myasthenia gravis (gMG) in the United States since the introduction of Soliris® in late 2017. Alexion is developing potential new therapies that leverage a similar mechanism of action are currently being tested in randomized controlled clinical trials.

A need exists for the collection of real-world data on effectiveness and patterns of patient care, including C5ITs, in the indicated population to complement the body of scientific evidence and better inform current and future clinical practice. Currently, there is no registry that collects adequate data on patients with gMG treated with C5IT in the standard clinical practice setting in the US. Data from this registry will provide evidence of any sustained clinical and quality of life (QOL) impacts of C5IT in the real-world setting and was designed to collect information on treatment patterns (such as drug discontinuation/ dose reduction and drug holiday) of C5IT and their impact on patients' status (ie, clinical outcomes, QOL, healthcare resource utilization).

The medical community requires additional information on long-term safety in terms of vaccination factors and pregnancy and pregnancy outcomes in this patient population. The Alexion gMG Registry will actively collect long-term clinical outcomes related to the treatment of gMG with C5IT, pregnancies and pregnancy outcomes, and vaccination status to characterize the long-term effectiveness and safety profile.

Data will continue to be collected after C5IT discontinuation or interruption through the end of the study period in patients who remain enrolled in the Registry to provide information on clinical outcomes, QoL, and burden of disease post-discontinuation with C5IT, and capture reasons for discontinuations, interruptions, and restarts. These data may be useful to inform professional guidelines about best practices for the long-term treatment of patients with gMG.

2.2. Background

Generalized myasthenia gravis is a rare, debilitating, autoimmune disease affecting the neuromuscular junction (NMJ). Most patients with gMG have autoantibodies directed at acetylcholine receptors, located within the NMJ, and are designated as "patients with acetylcholine receptor antibody positive [AChR Ab(+)] gMG". Binding of the AChR Ab is the trigger for the underlying pathophysiology of gMG in these patients. This binding results in impairment in acetylcholine receptor (AChR) signaling, accelerated endocytosis and degradation of AChRs and damage to NMJ muscle endplate morphology. The combined result can be profound impairment in neuromuscular transmission, with severe clinical consequences. Analysis of nonclinical data suggests that activated, terminal complement plays a role in the destruction of normal NMJ endplate morphology and impairment of neuromuscular transmission (Zhou 2007). Patients with gMG typically experience weakness in their ocular muscles and as the disease progresses, bulbar, limb and/or respiratory muscles may become impaired. Symptoms may include drooping eyelids, blurred vision, difficulty chewing or swallowing, weakness in the arms and legs and/or difficulty breathing.

Terminal complement-mediated cell damage and inflammation at the NMJ play a central role in the pathophysiology of autoimmune-mediated MG (Tüzün 2013). Inhibiting C5 enzymatic cleavage prevents the generation of the proinflammatory/prothrombotic complement activation products, C5a, and the cytolytic and proinflammatory/prothrombotic, MAC C5b-9, that are responsible for the inflammatory consequences of terminal complement activation.

The mechanism of action of C5 inhibitors as terminal complement inhibitors supports their use in the management of gMG mediated by complement-activating antibodies directed against the NMJ in both adults and children/adolescents. Soliris was approved for the treatment of gMG in patients who are anti-AChR Ab+ on 23 October 2017 in the US. Approval was based on evidence from a pivotal clinical study in adult patients with refractory AChR Ab+gMG (Study ECU-MG-301). Patients in these studies achieved clinically meaningful improvements in the Myasthenia Gravis Activities of Daily Living profile (MG-ADL) scores from Baseline to Week 26 based on a Worst-Rank analysis of covariance (ANCOVA) and absolute differences from Baseline in the same score. Soliris has received marketing authorization for the treatment of patients with refractory AChR Ab+gMG at the time of preparation of this protocol.

2.3. Benefit/Risk Assessment

There is no direct benefit to patients who participate in the Alexion gMG Registry, as all patients will be receiving care according to the standard clinical practice as indicated by their treating physician(s).

3. OBJECTIVES AND OUTCOMES

Objectives	Outcomes

• To describe the long-term clinical effectiveness and QoL benefit of C5IT
  − To collect long-term clinical outcome to supplement clinical trial data
  − To collect patient-reported outcomes (PROs) in accordance with clinical practice
• To describe the impact of C5 therapies (ie, discontinuation/switching/dose reduction)
  − To capture C5 therapies treatment patterns of care, patient characteristics, reasons and clinical outcomes associated with medication changes
  − To collect clinical data on patterns of drug-response
• To describe the long-term benefit-risk ratio
  − To collect pregnancy data and vaccination outcomes
• To describe patterns of use of concomitant therapy, rate/length of hospitalizations and hospital related resource utilization
  − To collect concomitant medication-use patterns (steroid and immunosuppressant therapy sparing outcomes)
  − To collect admission/discharge date, hospital setting, hospital ward/ER, and other hospitalization-related data
	Clinical Outcomes
	• Myasthenia Gravis Foundation of America (MGFA) class
	• MGFA Post Intervention Status (PIS)
	• Myasthenia Gravis Composite (MGC)
	• Manual Muscle Testing (MMT)
	• Physician-reported gMG exacerbations and crises
	• Serious adverse events (SAEs), including Neisseria infections
	• Pregnancy and neonatal outcomes
	
	Patient-Reported Outcomes
	• MG-ADL Score
	• Myasthenia Gravis Quality of Life 15-revised (MG QoL15-r) Score
	• Employment Status (part time/ full time/ unemployed, disabled, retired)
	
	Resource Use
	• gMG-related hospitalizations (gMG-related Emergency Room (ER) visits and overnight hospitalizations [admission diagnosis, date of admission/ discharge, intensive care unit (ICU) visits and discharge setting])
	
	Therapies
	• All C5IT dosing information (changes in dose; dose frequency, dose interruptions, discontinuations, restarts, reasons for discontinuation)
	• Targeted concomitant medications

4. ALEXION GMG REGISTRY DESIGN

4.1. Overall Design

This is a long-term, multicenter, observational, registry of patients with gMG who are treated with C5IT at the time of enrollment

At the time of enrollment in the Registry, patient records will be queried for retrospective information about the patient's medical history and gMG disease, with certain data requested or required within a defined time period prior to the patient's initiation of C5IT. Following enrollment, prospective data collection will be performed using data obtained as part of routine clinical care and through -PRO methods, as indicated in the Schedule of Data Collection and Registry Schematic (Section 1.2 and Section 1.3, respectively). Data will be collected using an electronic data capture (EDC) system. The duration of data collection for the Registry will be up to 5 years from the time the first patient is enrolled.

If an enrolled patient discontinues treatment with C5IT, data should be collected through the end of the registry period, if possible, in order to document clinical characteristics and patient outcomes post-C5IT discontinuation, change to other therapies, and/or interruption.

Investigators and physicians will perform the study according to current clinical practice in their center with currently available treatment resources and information and in accordance with the regulations and guidelines governing medical practice and ethics within the US.

4.2. Scientific Rationale for Registry Design

Generalized MG is a rare devastating inflammatory neuromuscular disorder. Soliris is a C5 inhibitor that was approved in the US for treatment of adult patients with gMG in 2017 and is the only Food and Drug Administration (FDA)-approved therapy for the treatment of gMG. This registry is designed to help collect patient information for patients with gMG treated with C5IT, and after discontinuation or interruption of C5IT treatment, in the US. The Registry aims to facilitate expansion of the current knowledge relevant to the treatment in gMG, inclusive of Soliris. The Registry will address the following through scientific publications: the long-term clinical effectiveness and QoL benefit, the impact of C5 therapies (ie, discontinuation/switching/dose reduction, the long-term benefit-risk ratio, the safety of C5IT related to pregnancy and pregnancy outcomes and vaccination outcomes, patterns of concomitant therapy use, and rate/length of hospitalizations and hospital-related resource utilization).

4.3. End of Registry Definition

Data will be collected for a period of up to 5 years from the date of the first patient enrollment.

5. Selection And Withdrawal Of Physicians

5.1. Physician Participation

5.1.1. Responsibilities

To be eligible for gMG registry participation, physicians should meet the following qualifications:

- Agree to comply with gMG registry processes.
- Agree to comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations or General Data Protection Regulation (GDPR), as applicable, and/or institution/country-specific subject privacy requirements, as applicable.

5.2. Physician Withdrawal

Should a physician leave his/her medical practice, Alexion and the Institutional Review Board (IRB) should be informed in advance, and another physician should be identified to whom patients will be referred. If the replacing physician is interested and the site and the physician are qualified to join the Registry, the new site will be trained on gMG registry processes and will assume registry responsibilities for patients enrolled in the gMG registry.

Patient data entered in the gMG registry will remain in the database.

6. Registry Population

Patients with a diagnosis of gMG who are treated with C5IT at time of enrollment, or have ever been treated with C5IT prior to enrollment, and meet the inclusion criteria and exclusion criteria in Section 6.1 and Section 6.2 below, are eligible for registry participation. An Informed Consent and Authorization must be obtained prior to enrollment where required under applicable laws and regulations.

Patients cannot be currently participating in an Alexion-sponsored interventional clinical study. Patients who have concluded participation in an Alexion-sponsored clinical study are eligible to enroll in this registry, and enrollment in the Registry will not exclude a patient from enrolling in a future clinical study.

6.1. Inclusion Criteria

Patients are eligible to be included in the Registry only if all of the following criteria apply:

Age

1. Patients ≥ 18 years of age at the time of enrollment.

Type of Patient

2. Patients with gMG who have ever received treatment with C5IT according to the label at the time of enrollment in the Registry.

Informed Consent

3. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Other Criteria

4. Patients must have all of the following historical data available (within 6 months prior to the initiation of C5IT) to be enrolled in the Registry
   - MGFA class (worst class to date)
   - MG-ADL Score
   - MGC

6.2. Exclusion Criteria

Patients currently enrolled in an Alexion-sponsored interventional clinical study for treatment of gMG cannot be enrolled in the Alexion gMG Registry while enrolled/participating in the clinical study for gMG therapy.

7. CONCOMITANT THERAPIES AND PROCEDURES

Targeted concomitant therapies and procedures to be collected retrospectively at enrollment in the Registry and prospectively during registry follow-up are outlined in the Schedule of Data Collection (Section 1.2) and Registry Schematic (Section 1.3), and detailed in Section 9.

8. PATIENT DISCONTINUATION/WITHDRAWAL

8.1. Patient Discontinuation/Withdrawal From the Registry

Participation in the gMG registry is voluntary. Patients may decline to participate or withdraw their consent at any time. In the event of a patient discontinuing from the Registry, previously collected data will continue to be available for analyses.

The Registry may be stopped by the Sponsor for any reason. A patient may be withdrawn from the Registry by Sponsor or the participating physician if:

1. The Registry is stopped by Sponsor
2. It is discovered that the patient did not meet the inclusion criteria for participation in the Registry
3. The clinical site and/or registry physician is no longer participating in the Registry

8.2. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

9. Registry Procedures and Data Collection

Data from patients participating in this registry will be collected as a result of routine clinical care and through PRO methods. Data will be entered as indicated in the Schedule of Data Collection (Section 1.2). If an enrolled patient discontinues treatment with C5IT, data should be collected through the end of the Registry period, if possible. Data will be collected using an EDC system. The duration of data collection for the Registry will be up to 5 years from the time the first patient is enrolled.

Data collected as part of the patient's routine clinical management and obtained before signing of the ICF, both prior to C5IT treatment, and after initiation of C5IT, will be collected.

9.1. Data Collection Frequency

Data relevant to gMG disease, prior to and following initiation with C5IT, will be collected retrospectively at the time of enrollment in the Registry.

Following enrollment, data will be collected on an ongoing basis for all enrolled patients in the Alexion gMG Registry. Data will be collected as per standard of care.

Participating physicians or delegates can enter data at any time however, they will be requested to complete the electronic case report form (eCRF) at a minimum of every quarter for the first year and every 6 months thereafter, providing all relevant data collected as part of routine clinical practice since the last completion of the eCRF. More frequent data entry may be required to support safety and/or key analysis needs.

9.2. Demographics and Medical History

The following will be collected for all patients enrolled in the gMG registry

- Patient demographics
- Targeted illnesses and co-morbid conditions such as diabetes, hypertension, and blindness collected retrospectively prior to registry enrollment and prospectively thereafter
- gMG medical history (eg, anti-AChR antibody status, disease onset and diagnosis, thymoma/thymectomy collected retrospectively prior to registry enrollment and prospectively)
- Targeted treatments and therapies (eg, intravenous immunoglobulin, immunomodulators, immunosuppressants [eg, rituximab], therapeutic plasma exchange, and any drug involved in the MG management or eventual co existing autoimmune diseases) collected retrospectively from 1 year prior to the start of C5IT through registry enrollment and prospectively through the duration of the Registry
- Soliris or C5 inhibitor therapy initiation date and treatment history

9.3. Effectiveness and Safety Outcomes

The following assessments are expected to be conducted as part of the standard of care for patients with gMG. Data will be collected from patient records at time of enrollment pertaining to the most recent assessment within 6 months of initiation of C5IT, and the most recent assessment prior to registry enrollment. All assessments done after enrollment in the Registry will be collected prospectively through the duration of the Registry.

- MGFA class
- MGFA PIS
- MGC
- MMT
- MG-ADL Score
- MG QoL15-r Score

In addition to the assessments listed above, physician-reported gMG exacerbations and crises (severity and duration) will be collected retrospectively for 1 year prior to the start of C5IT, if available, and prospectively.

9.4. Other Outcomes

The following items are expected to be collected as part of the standard of care for patients with gMG. All assessments done after enrollment in the Registry will be collected prospectively through the duration of the Registry.

- gMG-related hospitalizations (gMG-related ER visits) and overnight hospitalizations (admission diagnosis, date of admission/discharge, ICU visits and discharge status)
- Employment Status (part time/ full time/ unemployed, disabled, retired)
- All C5IT dosing information (changes in dose; dose frequency, dose interruptions, discontinuations, restarts, and reasons for changes, discontinuations, or restarts) collected retrospectively through registry enrollment and prospectively

9.5. Safety Data

9.5.1. Vaccination Status

Meningococcal vaccination information (date and type of vaccination) will be collected retrospectively as available through the registry enrollment and prospectively following enrollment.

9.5.2. Pregnancy and Breastfeeding Status

- Details of all pregnancies in female patients (enrolled in the Registry) and female partners of male patients (enrolled in the Registry) will be collected after signing of the ICF and until the end of data collection (for the Registry).

- If a pregnancy is reported, the physician should inform Alexion within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 11.2.
- Pregnancy and neonatal outcomes will be collected (see Section 9.5.3).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and should be reported to Global Drug Safety (GDS) within 24 hours of awareness.

9.5.3. Reporting Exposure During Pregnancy, Lactation, and Follow-up of Neonates

- All pregnancies in female patients receiving C5IT and in female partners of male patients receiving C5IT must be reported to Alexion GDS within 24 hours of the site's initial awareness. Although pregnancies are not considered SAEs, the physician is required to initially report all pregnancies by completing the "Pregnancy Reporting and Outcome Form and Breastfeeding form" and SAE email/fax coversheet. Registry sites should collect all information upon initial pregnancy awareness, each trimester, upon outcome of the pregnancy and at 3 months post-partum making sure to include any post-natal sequelae in the infant. This information should be sent to Alexion via email or fax:
  - Email: ClinicalSAE@alexion.com
  - Fax: + 1-203-439-9347

  Exposure of an infant to C5IT during breastfeeding will also be reported on the "Pregnancy Reporting and Outcome Form and Breastfeeding Form", and any adverse events an infant may experience following breastfeeding will be reported to Alexion GDS.

10. STATISTICAL CONSIDERATIONS

10.1. Statistical Hypotheses

This is an observational registry intended to characterize the clinical course and burden of disease of gMG while treated with C5IT and after C5IT discontinuation or interruption; thus, no statistical hypothesis testing is planned.

10.2. Number of Patients:

Up to 500 patients with gMG who are receiving treatment with C5IT will be enrolled in order to have adequate representation of the real-world experience of patients with gMG.

Invitations to participate in the Registry will be limited to physicians with ≥ 3 patients with gMG who are receiving treatment with C5IT at time of registry enrollment.

10.3. Statistical Analyses

Prior to the conduct of data analyses, details of planned analyses and patient cohorts will be prespecified in an Epidemiological and Statistical Analysis Plan (ESAP).

Categorical variables will be described using frequencies and percentages and may be modeled using logistic regression, while continuous variables will be described using means, standard deviations, medians, and/or inter-quartile ranges where appropriate, and modeling may be accomplished through generalized linear models, or other statistical techniques where appropriate. When pre-C5IT baseline data is available, evaluation of effectiveness will come from analysis of within-patient changes over time from Baseline.

The evaluation of safety will primarily come from descriptive summaries of SAEs.

Study results will be summarized and reviewed at appropriate intervals based on patient enrollment and scientific considerations.

Data analyses will be periodically conducted to meet requirements (if any) of regulatory agencies and reimbursement authorities and for support of scientific manuscripts and/or conference abstracts. Data may also be analyzed and reported at the request of registry physicians.

As part of analyses, patient disposition, the number of enrolled patients, and the number of discontinued patients (and reasons the patient discontinued) will be summarized. Analyses will assess effectiveness and safety outcomes, including occurrence and time-to-first event for safety outcomes. All outcomes will be described using relevant statistical summaries and their clinical interpretations will be provided.

Patients may discontinue and/or have an interruption from C5IT treatment but remain in the Registry with or without using other treatments. In general, the time during which patients are receiving treatment with C5IT will be included in person-years denominator when estimating rates of safety outcomes for C5IT, while the time they are not receiving C5IT will contribute to person-years of non-C5IT treatment (regardless of other treatment types).

The ESAP will describe in detail the methods and variables used in analyses, including those pertaining to truncated and missing data. Furthermore, the extent of missing or truncated data within the analysis datasets will be described in scientific presentations.

Following is a summary of planned analyses for data collected in the Registry. Precise details of analyses performed will be dependent on rate of patient enrollment and extent of data that are submitted to the Registry.

Demographics, Baseline Disease Characteristics, and Disposition

Descriptive summary statistics will be provided for demographics and baseline disease characteristics, where baseline will be defined as date of initiation of treatment with C5IT. Disposition, including the number of patients enrolled and the number of patients who discontinued at the time of analysis, will be tabulated.

Effectiveness of C5 Inhibition Therapy and Disease Burden of gMG

Disease scores will be summarized as observed values and changes or percentage changes from initiation of C5IT over time. Physician-reported gMG exacerbations and crises and hospitalizations will be tabulated and may be estimated as incidence rates and/or time-to-event analyses, while treated with C5IT and while not treated with C5IT (for patients with treatment discontinuations and/or interruptions).

Descriptive summary statistics will be provided for vaccination and pregnancy status and outcomes, where baseline will be defined as date of initiation of treatment with C5IT.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Appendix 1: Regulatory, Ethical, and Registry Oversight Considerations

11.1.1. Regulatory and Ethical Considerations

- This registry will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable laws and regulations applicable to Registries
  - The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB by the physician and reviewed and approved by the IRB before the Registry is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the Registry design.
- The physician will be responsible for the following:
  - Providing written summaries of the status of the Registry to the IRB as requested in accordance with the requirements, policies, and procedures established by the IRB
  - Providing oversight of the conduct of the Registry at the site following all applicable local regulations

11.1.2. Financial Disclosure

Physicians and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Physicians are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

11.1.3. Informed Consent Process

- The physician (or his or her representative) will explain the nature of the Registry to the patient (and/or his or her legally authorized representative) and answer all questions regarding the Registry.
- Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of 21

CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/Independent Ethics Committee (IEC) or study center.

- The site medical record must include a statement that written informed consent was obtained before the patient was enrolled in the Registry and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the Registry, if deemed appropriate by their IRB.
- A copy of the ICF(s) must be provided to the patient and/or the patient's legally authorized representative.

11.1.4. Data Protection

- Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his or her personal registry-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

11.1.5. Dissemination of Registry Data

Registry-related information may be posted on publicly accessible clinical study databases (eg, the US website www.clinicaltrials.gov or the EU website www.clinicaltrialsregister.eu), as appropriate, and in accordance with national, regional, and local regulations.

11.1.6. Data Quality Assurance

- All patient data relating to the Registry will be recorded on eCRFs. The physician is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).
- The physician must maintain accurate documentation (patient record) that supports the information entered in the eCRF.
- The physician must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide access to patient record, as applicable.
- The sponsor or designee is responsible for the data management of this registry including quality checking of the data as appropriate to real-world data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from patient records; that the rights of patients are being protected; and that

the data collection is being conducted in accordance with the currently approved protocol and any other study agreements and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this registry must be retained by the physician for 5 years after registry completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.1.7. Patient Records

- Patient records provide evidence for the existence of the patient and substantiate the integrity of the data collected. The physician or designee will prepare and maintain adequate and accurate patient records designed to record all observations and other pertinent data for each patient.
- Data entered in the eCRF that are transcribed from patient records must be consistent with the patient records or the discrepancies must be explained. The physician or designee may need to request previous medical records or transfer records. Also, current medical records must be available.

11.1.8. Scientific Advisory Committee

The Registry will be overseen by a Scientific Advisory Committee, comprised of expert clinicians involved in the research or care of patients with gMG. Examples of the Scientific Advisory Committees' activities will include, but not be limited to, advising on data analysis, authoring, and presenting registry data at medical conferences of relevant international and national professional societies as well as peer-reviewed publications. Publication of registry data will be subject to initial review and guidance from the Scientific Advisory Committee. Further details of roles and responsibilities of the Scientific Advisory Committee will be established in a charter.

The Scientific Advisory Committee will provide guidance to Alexion around the plan for regular publications based on analysis of global registry data, including the contents of such publications. For each publication, the Scientific Advisory Committee and Alexion will collaborate in guiding data analyses, interpretation of data analyses, and publication writing.

The Scientific Advisory Committee will be responsible for providing guidance to Alexion around publication proposals, analysis requests, and identifying journals, venues, and audiences of interest. Any participating registry physician may publish data analysis based on his/her own patient and any physician, including those not participating in the Registry, may submit for review an analysis request to support a publication. The Scientific Advisory Committee will provide guidance around the scientific merit of the analysis request and the alignment with the Registry publication strategy. Considerations around prioritizing the publication may include the academic and/or scientific importance of the questions and the source of the request (eg, participating registry physician, non-participating physician).

Participating physicians and patients will retain control of the patient data that they submit to the Registry and may use those data accordingly. Aggregate analyses will be the property of the

Alexion and will be disseminated according to this governance structure. Alexion retains the ability to use registry data for any regulatory or reimbursement requirements without obtaining prior approval from the committee.

11.2. Appendix 2: Collection of Pregnancy Information

Male Patients With Partners Who Become Pregnant

- The physician will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this registry.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the physician will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy and collection of signed informed consent. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 3 months following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Patients Who Become Pregnant

The physician will collect pregnancy information on any female patient who becomes pregnant while participating in this registry. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a patient's pregnancy. The patient will be followed to determine the outcome of the pregnancy. The physician will collect follow-up information on the patient and the neonate utilizing the GDS Pregnancy Reporting and Breastfeeding Outcome Form and the information will be forwarded to the sponsor. Global Drug Safety (GDS) requires follow-up at each trimester until the birth of the baby and the infant at 3-months postpartum. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the physician will be reported to the sponsor as described in Section 9.5.3. While the physician is not obligated to actively seek this information in former registry patients, he or she may learn of an SAE through spontaneous reporting.

11.3. Appendix 3: Abbreviations

Abbreviation or Specialist Term	Explanation
AChR	acetylcholine receptor
AChR Ab(+)	acetylcholine receptor antibody positive
ANCOVA	analysis of covariance
C5	complement component 5;
CIOMS	Council for International Organizations of Medical Sciences
CRF	case report form
eCRF	electronic case report form
EDC	electronic data capture
ER	emergency room
ESAP	Epidemiological and Statistical Analysis Plan
FDA	Food and Drug Administration
GDPR	General Data Protection Regulation
GDS	Global Drug Safety
gMG	generalized myasthenia gravis
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICU	intensive care unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MG QoL15-r	Myasthenia Gravis Quality of Life 15-revised
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGC	Myasthenia Gravis Composite
MGFA	Myasthenia Gravis Foundation of America
MMT	Manual Muscle Testing
NMJ	neuromuscular junction
PIS	MGFA Post Intervention Status
PRO	patient-reported outcome
SAE	serious adverse events
QoL	quality of life

12. REFERENCES

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