TITLE PAGE

Protocol Title: A Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Participants with Dermatomyositis.

Protocol Number: ALXN1210-DM-310

Amendment Number: 3.0

Compound: Ravulizumab (ALXN1210)

Study Phase: Phase 2/3

Brief Title: Ravulizumab versus Placebo in Adult Participants with Dermatomyositis

Sponsor Name: Alexion Pharmaceuticals, Inc.

Legal Registered Address: 121 Seaport Boulevard
Boston MA 02210
USA

Regulatory Agency Identifier Number(s)

IND Number: **152551**

EudraCT: **2021-001200-15** (formerly)

EU CT Number: **2023-503478-19-00**

Release Date: 23 Jun 2023

Sponsor Signatory:

[redacted] **Date**

Medical Monitor Name and Contact Information will be provided separately

INVESTIGATOR'S AGREEMENT

I have read the study protocol and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Guideline for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

This summary indicates the major changes made to Protocol ALXN1210-DM-310, Amendment 2.0.

Amendment 3 (23 Jun 2023)

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC and in the EU CTR 536/2014 Article 2, 2 (13).

Overall Rationale for the Amendment:

The primary reasons for this modification are:
The extension of the Randomized Controlled Period (RCP) of study Part B (Phase 3) from 26 weeks to 50 weeks. Extension for approximately 1 year will allow for prolonged assessment of the effects of ravulizumab versus placebo in adult participants with DM, given that DM is a progressive chronic condition. This extension will also be in line with regulatory authority requests.
The extension of the Open-Label Extension Period (OLE) of study Part A (Phase 2) from 74 weeks up to 130 weeks to ensure treatment continuity for patients.

Additionally, modifications have been added to address the requirements for conducting a clinical study under the European Union Clinical Trials Regulation (EU CTR).
Further modifications include nonsubstantial changes, minor corrections, and harmonized terminology.

Section # and Name	Description of Change	Brief Rationale
Modifications describing the extended Open-Label Extension Period (OLE) Period of study Part A and the extended Randomized Controlled Period (RCP) of study Part B		
Section 1.1 Synopsis Section 3 Objectives, Estimands and/or Endpoints	Changed study Part B endpoints for the RCP from Week 26 to Week 50 assessments. Changed endpoints/estimands for the OLE Periods from Week 100 to Week 156 (Part A) and from Week 100 to Week 124 (Part B).	Extension of Part B RCP to a duration of 50 weeks based on regulatory authority (FDA) request. To reflect extension of study Part A OLE Period up to 130 weeks.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Overall Design, Section 1.2 Schema, Section 4.1 Overall Design, Section 4.2.1 Study Population and Treatment Duration, Section 6.3.2 Blinding, Section 6.5.3 Acute Therapy with Standard DM Treatment, Section 9 Statistical Considerations, and throughout protocol	Changed study Part B RCP duration from 26 weeks to 50 weeks for a total duration of study Part B of up to 124 weeks (approximately 2.5 years).	Extension of Part B RCP to a duration of 50 weeks based on regulatory authority (FDA) request.
Section 1.1 Synopsis, Overall Design, Section 1.2 Schema, Section 4.1 Overall Design, and throughout protocol	Changed study Part A OLE Period from 74 weeks up to 130 weeks for a total duration of study Part A of up to 156 weeks (approximately 3 years).	To reflect extension of study Part A OLE Period up to 130 weeks.
Section 1.1 Synopsis, Intervention Groups and Duration, Section 4.4 End of Study Definition	Added additional exit options for participants discontinuing from the study before end of the OLE Period: Participants may continue to receive ravulizumab until either: a) The end of the respective OLE Period b) Ravulizumab is registered or approved (in accordance with country-specific regulations), c) An alternative option for example transition to a rollover study or an early access program is provided	To provide an exit strategy for participants discontinuing from the study before end of the OLE Period.
Section 1.3 Schedule of Activities, Table 2	Added a separate schedule of activities (SoA) table for study Part B RCP to account for the additional study visits during the extended RCP.	Extension of Part B RCP to a duration of 50 weeks based on regulatory authority (FDA) request.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities, Table 3, Table 4, and Table 5	Added 2 additional separate SoA tables for study Part A OLE to account for the additional study visits during the extended OLE Period. Updated Table 5 (Part B, OLE) to reflect updated study visit days.	To reflect extension of study Part A OLE Period up to 130 weeks. To reflect changed study visit days in Part B OLE based on extended Part B RCP.
Section 6.1.1. Study Intervention(s) Administered, Table 12 and Table 13	Adjusted study intervention dosing days to the extended OLE Period of study Part A and extended RCP of study Part B.	To reflect extension of study Part B RCP to 50 weeks and extension of study Part A OLE Period up to 130 weeks.
Requirements for conducting a clinical study under the European Union Clinical Trials Regulation (EU CTR)		
TITLE PAGE and Section 1.1 Synopsis	Added regulatory agency identifier number (EU CT number). Changed Short Title to **Brief Title.**	Updated in accordance with EU CTR.
Section 1.1 Synopsis	Added text on Ethical Considerations and Benefit-Risk Assessment. Added Brief Summary of synopsis comprising study Part A and Part B.	Updated in accordance with EU CTR.
Section 2.3.1 Risk Assessment	Updated wording on immunogenicity risk mitigation strategy.	To clarify instructions to Investigators in case of potential immunogenicity reactions.
Section 3.1.1 Primary Estimand for Part A and throughout protocol	Change of terminology: "stable background DM treatments" to "**stable allowed concomitant DM treatments**"; modified throughout document.	Updated in accordance with EU CTR.
Section 6.1 Study Intervention(s) Administered	Added AxMP = auxiliary medicinal product.	Updated in accordance with EU CTR.
Section 6.2 Preparation/Handling/Storage/ Accountability	Added details on study intervention accountability.	Updated in accordance with EU CTR.
Section 6.5.3 Acute Therapy with Standard DM Treatment (formerly: Rescue Therapy) and throughout protocol	Change of terminology: "rescue therapy" to "**acute therapy with standard DM treatment**"; modified throughout document.	Updated in accordance with EU CTR.

Section # and Name	Description of Change	Brief Rationale
Section 8.3.4 Regulatory Reporting Requirements for SAEs, Section 10.4.5 Unexpected Events	Described reporting requirements and provided definition of unexpected events, respectively.	Updated in accordance with EU CTR.
Section 8.3.5 and Section 10.5, Medication Error, Drug Abuse, and Drug Misuse	Provided definition and examples of medication error, drug abuse, and drug misuse and described reporting requirements.	Updated in accordance with EU CTR.
Section 8.4 Treatment of Overdose	Described reporting requirements.	Updated in accordance with EU CTR.
Section 8.5 Pharmacokinetics and Pharmacodynamics, Section 8.7.1 Blood Exploratory Biomarkers. Section 8.7.2 Additional Biomarker Research, Section 8.8 Immunogenicity Assessments, Section 10.2.1 Regulatory and Ethical Considerations, Section 10.2.5 Data Protection, Section 10.2.7 Quality Data Assurance	Added additional details on data collection, data storage, and data protection. Specified that applicable regulations will apply. Specified that serious breaches will include data breaches compromising the integrity, confidentiality, or availability of the personal data of participants. Outlined measures in case of personal data breaches. Added that unique identifiers will be assigned to participants by a Trusted Third Party contracted by Alexion or by a Principal Investigator. Specified that personal study-related data will also be decoded (pseudonymized). Added paragraphs detailing data protection regulations and measures to protect coded study data. Added details on legal protection of participant data. Specified storage requirements for study data/documents (at least 30 years after study completion).	Updated in accordance with EU CTR and as per RFI received for another Alexion clinical study with ravulizumab.

Section # and Name	Description of Change	Brief Rationale
Section 10.2.1 Regulatory and Ethical Considerations	Added definition and process for reporting serious breaches. Removed statement on UK regulations. Removed **substantial**: The protocol, ~~substantial~~ protocol amendments …	Updated in accordance with EU CTR. UK-specific regulations are now covered under country-specific regulations as per EU CTR.
Section 10.2.4 Recruitment Strategy	Added new section to describe recruitment strategy for the study.	Updated in accordance with EU CTR.
Section 10.2.5 Data Protection	Added paragraphs which outline requirement for a) Data protection and handling responsibilities between Alexion and study site(s) to be captured in contract b) Information technology systems to ensure data protection	Updated in accordance with EU CTR.
10.2.7 Data Quality Assurance	Specified: Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for **at least 30 years** after study completion or longer as per local regulations or institutional policies.	Updated in accordance with EU CTR.
Section 10.2.9 Study and Site Start and Closure	Clarified study start date as the date on which the clinical study will be open for recruitment of participants (ie, first site activation).	Updated in accordance with EU CTR.
Other substantial changes, nonsubstantial changes, corrections, and harmonized terminology		
Section 1.1 Synopsis, Overall Design, Section 4.1.1 Part A (Phase 2 Portion) Section 4.1.2 Part B (Phase 3 Portion)	Modified statement: Participants (in the OLE Period) who discontinue study intervention~~will~~ **are encouraged to** complete the visits and assessments of the OLE Period.	For clarification.
Section 1.3 SoA, Table 1	Added urinalysis and clinical laboratory tests on Day 15	Correction.
Section 1.3 SoA, Table 2	“Ravulizumab infusion” was added for Unscheduled Visits	Addition to ensure consistency with respective footnote.

Section # and Name	Description of Change	Brief Rationale
Section 3.1.1.1 Primary Analysis for Part A	Discontinuation of study intervention due to death added as an intercurrent event.	Ensures missing data following death would be considered a non-responder for the primary analyses in Parts A and B.
Section 4.1.3 Clinical Worsening	Specified that clinical worsening criteria will be assessed at the visits described in Section 1.3 until the End of Study for all parts of the study. Rearranged section.	For clarification, understandability, and increased patient centricity.
Section 4.3 Justification for Dose	Specified that ravulizumab dosing regimen is identical to approved weight-based dosing and is targeting immediate, complete and sustained inhibition of terminal complement.	For clarification.
Section 5.2 Exclusion Criteria; Criteria #1	Changed: "(except basal or squamous cell skin cancer or carcinoma in situ of the cervix that has been excised and cured **and** at least 3 months before Screening)." **to** "(except basal or squamous cell skin cancer or carcinoma in situ of the cervix that has been excised and cured **for** at least 3 months before Screening)."	Correction.
Section 6.1.1 Study Intervention(s) Administered Section 6.1.1.1 Part A Section 6.1.1.2 Part B	Added statement that the initial loading dose will be administered at the beginning of the RCP and the OLE followed by maintenance dosing initiated 2 weeks after loading dose. Changed: "…will receive open-label ravulizumab … until the end of the OLE Period" to "…**until the last scheduled dose at Week 148**" (Part A) and "…**until the last scheduled dose at Week 116**" (Part B).	Modified for clarification and to reflect the modified study design.

Section # and Name	Description of Change	Brief Rationale
Section 6.3.2 Blinding Section 9.5.1 Part A Interim Analyses	Unblinded information will ~~only~~ be accessible to those who need to be involved in the safety reporting to Health Authorities, Independent Ethics Committees (IECs), Institutional Review Boards (IRBs), and/or IDMC. Moved information on discontinuation of unblinded participants to the end of the section. Added statement on potential additional analyses in Part A (at the time of the interim analyses) which may be generated and reviewed by an unblinded team (independent of the study team).	Correction and for transparency.
Section 6.5.1.2 Other Allowed Therapies	Changed "below" to "above": "However, participants taking the medications listed ~~below~~ above at a stable dose for at least 4 weeks before Screening are allowed to continue these medications." The modification is also captured in administrative letter 3.	Correction.
Section 7.1 Discontinuation of Study Intervention	Specified that the Investigator's decision to discontinue study intervention should be based on a documented safety concern or AE or lack of improvement. Added that discontinuation of study intervention should also be considered in case of Clinical Worsening. Corrected hyperlink to Section 6.5.3 for acute therapy with standard DM treatment.	Modified for clarification. Correction.
Section 7.2 Participant Discontinuation/Withdrawal from the Study	Specified that consent can be withdrawn by a participant at any time, and removed possibility for participant withdrawal by the Investigator.	Update based on FDA feedback.
Section 8.1.11 Handheld Dynamometry	Handheld dynamometry will be assessed at ~~screening and~~ timepoints specified in the SoA.	Correction, alignment with SoA.

Section # and Name	Description of Change	Brief Rationale
Section 8.1.9 Dermatomyositis Disease Symptoms Questionnaire (DM-DSQ), Section 10.8.13 Dermatomyositis Disease Symptoms Questionnaire (DM-DSQ)	Added that DM-DSQ version 1.1 will be used in the Part A RCP and OLE Period while DM-DSQ version 5.0 will be used in the Part B RCP and OLE Period.	Clarification.
Section 8.8 Immunogenicity Assessments	Specified that **validated** rather than **validated/qualified** assays will be used.	Correction according to current immunogenicity wording.
Section 9.3 Populations for Analyses, Table 17; Section 9.4.3.2 Analysis of Immunogenicity	Changed ADA Analysis Set (AAS) to **Immunogenicity Analysis Set (IAS)**. Specified that immunogenicity results will be analyzed by summarizing the number and percentage of participants ~~who develop confirmed positive ADAs~~ **according to their ADA response status.**	Updated terminology.
9.4.1.1.1. Analyses of Primary Efficacy Endpoint for Part A	Revised primary analysis to remove weighted Generalized Estimating Equations (wGEE) model and replace with Barnard's unconditional exact test for difference of proportions.	Revised method proposed to simplify the statistical inference and to enable use of single imputation for missing TIS data.
Section 9.4.1.1.2 Analyses of Secondary Efficacy Endpoint for Part A	Removed wGEE and logistic model for secondary endpoints in Part A.	To align analysis method for secondary binary endpoints with the primary endpoint
Section 9.4.1.2.1 Analyses of Primary Efficacy Estimand and/or Endpoint for Part B	Revised primary analysis from wGEE to a Cochran-Mantel Haenszel (CMH) test with Multiple Imputation (MI) for missing data not due to intercurrent events.	Revised method to simplify the statistical inference and to enable use of multiple imputation for missing TIS data.
Section 9.4.1.2.2 Sensitivity Analysis for the Primary Estimand for Part B	Removed reference of observation weighting Edits to purpose of the sensitivity analyses.	No longer applicable due to revised primary endpoint analysis, For clarification of sensitivity analyses.

Section # and Name	Description of Change	Brief Rationale
Section 9.4.1.2.4 Analyses of Key Secondary Efficacy Endpoint(s) for Part B	Removed adjusted baseline covariates.	To align with revised approach in 9.4.1.2.1
Section 9.4.1.2.5 Multiplicity Adjustment for Part B	Minor edits.	For clarification.
Section 9.5.1 Part A Interim Analyses	Added statement on potential additional analysis in Part A (at the time of the interim analysis which may be generated and reviewed by an unblinded team (independent of the study study).	For clarification .
Section 9.5.2 Part B Interim Analyses	Revised the Sample Size Reestimation (SSR) to align with the primary endpoint and changed the percentage of participants from 50% to 30%. Further clarification regarding SSR.	To align with revised primary endpoint and to include additional details of SSR for clarification.
Section 9.6 Data Monitoring Committee	Corrected DMC to **IDMC** in 2 instances as IDMC is used for study.	Correction.
Section 10.2.6 Dissemination of Study Data	Outlined that the results will be posted after the global end of the study.	For clarification.
Section 10.8 Clinical Outcome Assessment	Changed appendix header from ~~Participant-Reported Outcome Instruments~~ to **Clinical Outcome Assessments**	Modified appendix heading to reflect clinical assessment of outcome measures.
Throughout	Specified **Phase 2** for study Part A and **Phase 3** for study Part B where applicable.	For clarification.
Throughout	Orthographic corrections were made throughout the document.	Correction.

Abbreviations: ADA = antidrug antibody; AE = adverse event; DM = dermatomyositis; DMC = Data Monitoring Committee; ICF = informed consent form; IDMC = Independent Data Monitoring Committee; SAE = serious adverse event

TABLE OF CONTENTS

TITLE PAGE 1
INVESTIGATOR'S AGREEMENT 2
PROTOCOL AMENDMENT SUMMARY OF CHANGES 3
TABLE OF CONTENTS 12
LIST OF TABLES 18
LIST OF FIGURES 19
1. PROTOCOL SUMMARY 20
1.1. Synopsis 20
1.2. Schema 28
1.3. Schedule of Activities 29
2. INTRODUCTION 58
2.1. Study Rationale 58
2.2. Dermatomyositis Background 59
2.2.1. Abnormal Complement Activation in DM Pathogenesis 59
2.3. Benefit/Risk Assessment 60
2.3.1. Risk Assessment 61
2.3.1.1. Coronavirus Disease 2019 62
2.3.2. Benefit Assessment 62
2.3.3. Overall Benefit: Risk Conclusion 62
3. OBJECTIVES AND ESTIMANDS AND/OR ENDPOINTS 63
3.1. Primary Estimand(s) 71
3.1.1. Primary Estimand for Part A 71
3.1.2. Primary Estimand for Part B 72
3.2. Secondary Estimands 72
3.3. Exploratory Estimands 72
4. STUDY DESIGN 73
4.1. Overall Design 73
4.1.1. Part A (Phase 2 Portion) 73
4.1.2. Part B (Phase 3 Portion) 74
4.1.3. Clinical Worsening 75
4.1.4. Completion of Treatment 75

4.1.5. Completion of Randomized Controlled Period and OLE Period 76
4.2. Scientific Rationale for Study Design 76
4.2.1. Study Population and Treatment Duration 76
4.2.2. Rationale for Primary Endpoint: International Myositis Assessment and Clinical Studies-Total Improvement Score (IMACS-TIS) 77
4.2.3. Rationale for Secondary Endpoints included in the Multiplicity Adjustment for Part B 78
4.2.4. Participant Input into Design 78
4.3. Justification for Dose 78
4.4. End of Study Definition 78
5. STUDY POPULATION 80
5.1. Inclusion Criteria 80
5.2. Exclusion Criteria 81
5.3. Lifestyle Considerations 83
5.3.1. Meals and Dietary Restrictions 83
5.3.2. Activity 83
5.4. Screen Failures 83
6. STUDY INTERVENTION 84
6.1. Study Intervention(s) Administered 84
6.1.1. Study Intervention(s) Administered 85
6.1.1.1. Part A 90
6.1.1.2. Part B 90
6.2. Preparation/Handling/Storage/Accountability 91
6.3. Measures to Minimize Bias: Randomization and Blinding 92
6.3.1. Randomization 92
6.3.2. Blinding 93
6.4. Study Intervention Compliance 94
6.5. Concomitant Therapy 94
6.5.1. Allowed Medicine and Therapy 94
6.5.1.1. Dermatomyositis Treatment 94
6.5.1.2. Other Allowed Therapies 96
6.5.2. Disallowed Medicine and Therapy 97
6.5.3. Acute Therapy with Standard DM Treatment 97

6.6. Dose Modification 98
6.7. Intervention After the End of the Study 99
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 100
7.1. Discontinuation of Study Intervention 100
7.2. Participant Discontinuation/Withdrawal from the Study 101
7.3. Lost to Follow-up 101
8. STUDY ASSESSMENTS AND PROCEDURES 103
8.1. Efficacy Assessments 103
8.1.1. International Myositis Assessment and Clinical Studies (IMACS) Core Set Measures (CSM) 103
8.1.1.1. Myositis Disease Activity Assessment Tool (MDAAT) 103
8.1.1.2. Physician Global Activity Assessment 103
8.1.1.3. Patient Global Activity Assessment 104
8.1.1.4. Manual Muscle Testing 8 Muscles Group (MMT-8) 104
8.1.1.5. Health Assessment Questionnaire (HAQ) 104
8.1.1.6. Muscle Enzymes 104
8.1.2. Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) 104
8.1.3. Cutaneous Dermatomyositis Activity Physician's Global Assessment (CDA-IGA) 104
8.1.4. EuroQoL 5 Dimensions (EQ-5D-5L) 105
8.1.4.1. EQ-5D-5L Descriptive System 105
8.1.4.2. EQ Visual Analog Scale 105
8.1.5. 5D-Itch Scale 105
8.1.6. Patient-Reported Outcomes Measurement Information System (PROMIS) 29 v2.1 Tool 105
8.1.7. Short Form Health Survey (36 Questions Version) (SF-36) 105
8.1.8. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) 106
8.1.9. Dermatomyositis Disease Symptoms Questionnaire (DM-DSQ) 106
8.1.10. 30-Second Chair Stand Test (30s CST) 106
8.1.11. Handheld Dynamometry 106
8.1.12. Home Electronic Patient-Reported Outcomes 107
8.2. Safety Assessments 107
8.2.1. Vaccine and Antibiotic Prophylaxis 107

8.2.2. Physical Examinations 107
8.2.3. Height and Weight 108
8.2.4. Vital Signs 108
8.2.5. Electrocardiograms 108
8.2.6. Clinical Safety Laboratory Assessments 108
8.2.7. Pregnancy 109
8.2.8. Participant Safety Card 109
8.3. Adverse Events and Serious Adverse Events 110
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 110
8.3.2. Method of Detecting AEs and SAEs 110
8.3.3. Follow-up of AEs and SAEs 110
8.3.4. Regulatory Reporting Requirements for SAEs 110
8.3.5. Medication Error, Drug Abuse, and Drug Misuse 111
8.3.5.1. Timelines 111
8.3.5.2. Medication Error 111
8.3.5.3. Drug Abuse 111
8.3.5.4. Drug Misuse 111
8.3.6. Adverse Events of Special Interest 111
8.4. Treatment of Overdose 112
8.5. Pharmacokinetics and Pharmacodynamics 112
8.6. Genetics 113
8.7. Biomarkers 113
8.7.1. Blood Exploratory Biomarkers 113
8.7.2. Additional Biomarker Research 113
8.8. Immunogenicity Assessments 113
8.9. Health Economics Data and/or Medical Resource Utilization 114
8.10. Other Assessments and Procedures 114
8.10.1. Medical History and DM History and Diagnosis 114
9. STATISTICAL CONSIDERATIONS 115
9.1. Statistical Hypotheses 115
9.2. Sample Size Determination 115
9.2.1. Part A 115
9.2.2. Part B 115

9.3. Populations for Analyses 115
9.4. Statistical Analyses 116
9.4.1. Efficacy Analyses 116
9.4.1.1. Efficacy Analysis of Part A 117
9.4.1.2. Efficacy Analysis of Part B 117
9.4.2. Safety Analyses 119
9.4.2.1. Analysis of Adverse Events 119
9.4.2.2. Analysis of Clinical Laboratory Parameters, Vital Sign Measurements, and ECG Parameters 120
9.4.3. Other Analyses 120
9.4.3.1. Pharmacokinetic/Pharmacodynamic Analysis 120
9.4.3.2. Analysis of Immunogenicity 120
9.4.3.3. Analysis of Biomarkers 120
9.4.3.4. Analyses of Exploratory Endpoint(s) 120
9.5. Interim Analyses 121
9.5.1. Part A Interim Analysis 121
9.5.2. Part B Interim Analysis 121
9.6. Data Monitoring Committee 121
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 122
10.1. Management of Potential Infusion-Associated Adverse Events During Study Intervention Administration 122
10.2. Regulatory, Ethical, and Study Oversight Considerations 124
10.2.1. Regulatory and Ethical Considerations 124
10.2.2. Financial Disclosure 126
10.2.3. Informed Consent Process 126
10.2.4. Recruitment Strategy 127
10.2.5. Data Protection 127
10.2.6. Dissemination of Clinical Study Data 128
10.2.7. Data Quality Assurance 129
10.2.8. Source Documents 129
10.2.9. Study and Site Start and Closure 130
10.2.10. Publication Policy 131

10.2.11. Good Clinical Practice Compliance 131
10.3. Clinical Laboratory Tests 133
10.4. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 135
10.4.1. Definition of AE 135
10.4.2. Definition of SAE 136
10.4.3. Recording and Follow-Up of AE and/or SAE 137
10.4.4. Reporting of SAEs 139
10.4.5. Unexpected Events 139
10.5. Medication Error, Drug Abuse, and Drug Misuse 140
10.6. Contraceptive Guidance and Collection of Pregnancy Information 142
10.6.1. Definitions 142
10.6.2. Contraception Guidance 142
10.6.2.1. Guidance for Female Participants 143
10.6.2.2. Guidance for Male Participants 144
10.6.3. Collection of Pregnancy Information 144
10.6.3.1. Male Participants with Partners Who Become Pregnant 145
10.6.3.2. Female Participants Who Become Pregnant 145
10.7. Biomarkers 147
10.8. Clinical Outcome Assessments 148
10.8.1. Myositis Disease Activity Assessment Tool (MDAAT) 148
10.8.2. Physician Global Activity Assessment 152
10.8.3. Patient Global Activity Assessment 153
10.8.4. Manual Muscle Test (MMT-8) 154
10.8.5. Health Assessment Questionnaire (HAQ) 155
10.8.6. Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) 157
10.8.7. Cutaneous Dermatomyositis Activity Physician's Global Assessment (CDA-IGA) 158
10.8.8. EuroQoL 5 Dimensions (EQ-5D-5L) 159
10.8.8.1. EQ-5D-5L Version for In-Clinic Use 159
10.8.9. 5D-Itch Scale 162
10.8.10. PROMIS-29 v2.1 Tool 163
10.8.11. Short Form Health Survey (36 Questions Version) (SF-36) 166

10.8.12. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) 172
10.8.13. Dermatomyositis Disease Symptoms Questionnaire (DM-DSQ) v1.1 and v5.0 173
10.8.14. 30-Second Chair Stand 177
10.9. COVID-19 Risk Assessment 178
10.10. COVID-19 Vaccine Risk Assessment 180
10.11. Abbreviations 181
10.12. Protocol Amendment History 185
11. REFERENCES 186

LIST OF TABLES

Table 1: Schedule of Activities: Screening Through End of the Randomized Controlled Period for Part A (Phase 2) 29
Table 2: Schedule of Activities: Screening Through End of the Randomized Controlled Period for Part B (Phase 3) 37
Table 3: Schedule of Activities: Open-Label Extension Period for Part A (Phase 2) – Week 26 to Week 100 45
Table 4: Schedule of Activities: Open-Label Extension Period for Part A (Phase 2) – Week 108 – Week 156 49
Table 5: Schedule of Activities: Open-Label Extension Period for Part B (Phase 3) 52
Table 6: Ravulizumab Identified and Potential Risks 61
Table 7: Mapping Objectives to Endpoints for Part A (Phase 2 Portion) 63
Table 8: Mapping Objectives to Endpoints/Estimands for Part B (Phase 3 Portion) 66
Table 9: Mapping Objectives to Endpoints/Estimands for Open-Label Extension (Part A and Part B) 69
Table 10: Study Intervention 84
Table 11: Weight-based Doses of Ravulizumab 85
Table 12: Reference Chart for Weight-based Dosing – Study Part A 86
Table 13: Reference Chart for Weight-based Dosing – Study Part B 88
Table 14: Allowed Concomitant DM Treatments 95
Table 15: Washout Periods Required Before Day 1 Visit 95
Table 16: Washout Periods Required Before Day 1 for Prohibited Medications 97
Table 17: Study ALXN1210-DM-310 Analysis Populations 115
Table 18: Clinical Criteria for Diagnosing Anaphylaxis 122

Table 19: Laboratory Assessments 133
Table 20: Potential Risks and Mitigation Measures Due to COVID-19.....178
Table 21: Potential Risks and Mitigation Measures Due to COVID-19 Vaccine 180
Table 22: Abbreviations and Specialist Terms 181

LIST OF FIGURES

Figure 1: Study Design Schematic 28

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Participants with Dermatomyositis.

Brief Title: Ravulizumab versus Placebo in Adult Participants with Dermatomyositis

Regulatory Agency Identifier Number(s):
IND Number: **152551**

EudraCT: **2021-001200-15** (formerly)

EU CT Number: **2023-503478-19-00**

Rationale:

Complement-mediated injury has been implicated in the pathology of dermatomyositis (DM), a disorder characterized by distinct skin rashes and muscle weakness (Dalakas, 2015; Isak, 2018; Mahil, 2012). Patients with DM typically present with proximal muscle weakness and cutaneous manifestations that develop over weeks to months (Selva-O'Callaghan, 2018). Muscle biopsies from patients with DM reveal the presence of membrane attack complex (MAC) on the endothelial cells of the endomysial capillaries (Dalakas, 2020; Kissel, 1986) indicating the involvement of complement component 5 (C5) in DM and providing the therapeutic rationale for use of C5 inhibitors in DM. Currently, there are only 3 therapies approved for the treatment of DM: azathioprine, corticotropin injections, and glucocorticoids. Additionally, a human plasma-derived intravenous immunoglobulin (IVIg) was recently approved for the treatment of DM in the EU and US. Despite therapy, however, about a third of patients with DM are left with mild to severe disability (Dalakas, 2003) and half of patients considered to be stable do not return to previous levels of work (Marie, 2001).

Ravulizumab is a recombinant, humanized monoclonal antibody (mAb) with high specificity against human C5 and blocks the cleavage of C5 into the pro-inflammatory complement component 5a (C5a) and the pro-inflammatory and lytic terminal complement complex (C5b-9).

Ravulizumab has been shown to achieve immediate, complete, and sustained terminal complement inhibition as a chronic treatment in patients with paroxysmal nocturnal hemoglobinuria (PNH), in patients with atypical hemolytic uremic syndrome (aHUS), in adult patients with generalized myasthenia gravis (gMG), and it is currently being developed as a treatment in several other complement-related indications. It is expected that the same dosing regimen approved for PNH, aHUS, and gMG will achieve comparable inhibition of complement-mediated damage in patients with DM. The combination of clinically relevant outcomes with terminal complement inhibition in other complement-mediated diseases and pharmacodynamic (PD) effects of ravulizumab on terminal complement provide the rationale for the hypothesis that ravulizumab may improve the clinical manifestations of DM in patients, and in particular, lead to a reduction in muscle weakness and cutaneous manifestations.

The objective of this study is to investigate the efficacy, safety, pharmacokinetics (PK), PD, and immunogenicity of ravulizumab in adult participants with DM.

Objectives and Estimands and/or Endpoints

Mapping Objectives to Endpoints/Estimands for Part A (Phase 2 Portion)

Objectives	Endpoints/Estimands
Primary	
To determine the effect of ravulizumab compared with placebo in the treatment of DM based on improvement in Total Improvement Score (TIS) IMACS-TIS[a]	IMACS-TIS[a] (TIS40) response at Week 26 of the Randomized Controlled Period as per defined composite estimand
Secondary	
To assess the efficacy of ravulizumab compared with placebo in the treatment of DM based on improvement in efficacy endpoints	• TIS at Week 26 • Change from baseline in CDASI Activity Score at Week 26 • Change from baseline in 5 IMACS core set measures (extra-muscular disease activity based on MDAAT, physician global activity assessment, patient global activity assessment, MMT-8, HAQ) at Week 26 • Response related to muscle enzymes: - normalization of most abnormal baseline enzyme at Week 26 • CDASI response (7-point improvement from baseline) at Week 26 • CDA-IGA response (almost clear or clear) at Week 26 • TIS20 response at Week 26 • TIS60 response at Week 26 • Time to First Response of TIS20, TIS40, or TIS60, respectively • Clinical worsening during RCP at 2 consecutive visits • Receipt of acute therapy with standard DM treatment
PK/PD/Immunogenicity	
To characterize the PK/PD and immunogenicity of ravulizumab in adult participants with DM	• Serum ravulizumab concentrations over the study duration • Change in serum free and total C5 concentrations over the study duration • Incidence and titer of ADAs over the study duration

Objectives	Endpoints/Estimands
Safety	
To characterize the overall safety of ravulizumab in participants with DM	• Incidence of TEAEs, TESAEs, and TEAEs leading to study intervention discontinuation

[a] ACR/EULAR-TIS

Abbreviations: ACR/EULAR = American College of Rheumatology/European League Against Rheumatism; ADA = antidrug antibody; C5 = complement component 5; CDASI = Cutaneous Dermatomyositis Disease Area and Severity Index; DM = dermatomyositis; CDA-IGA = Cutaneous Dermatomyositis Activity Physician's Global Assessment; HAQ = health assessment questionnaire; IMACS-TIS = International Myositis Assessment and Clinical Studies-Total Improvement Score; MDAAT = Myositis Disease Activity Assessment Tool; MMT-8 = manual muscle testing subset of 8 muscles; PD = pharmacodynamic(s); PK = pharmacokinetic(s); RCP = Randomized Controlled Period; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; TIS20 =TIS value ≥ 20-point improvement response on IMACS-TIS; TIS40 = TIS value ≥ 40-point improvement response on IMACS-TIS; TIS60 = TIS value ≥ 60-point improvement response on IMACS-TIS

Mapping Objectives to Endpoints/Estimands for Part B (Phase 3 Portion)

Objectives	Endpoints/Estimands
Primary	
To determine the effect of ravulizumab compared with placebo in the treatment of DM based on improvement in Total Improvement Score (TIS) IMACS-TIS)[a]	IMACS-TIS[a] (TIS40) response at Week 50 of the Randomized Controlled Period as per defined composite estimand
Key Secondary	
To assess the efficacy of ravulizumab compared with placebo in the treatment of DM based on improvement in components of IMACS and other myositis activity measures	• TIS at Week 50 • Change from baseline in MMT-8 at Week 50 • Change from baseline in extra-muscular disease activity based on MDAAT at Week 50 • Change from baseline in CDASI Activity Score at Week 50
Secondary	
To assess the efficacy of ravulizumab compared with placebo in the treatment of DM based on other efficacy endpoints	• Change from baseline in 3 IMACS core set measurements (physician global activity score, patient global activity score, HAQ) at Week 50 • Response related to muscle enzymes: - normalization of most abnormal baseline enzyme at Week 50 • CDASI response (7-point improvement from baseline) at Week 50 • CDA-IGA response (almost clear or clear) at Week 50 • TIS20 response at Week 50 • TIS60 response at Week 50 • Time to First Response of TIS20, TIS40, or TIS60, respectively • Clinical worsening during RCP at 2 consecutive visits • Receipt of acute therapy with standard DM treatment

Objectives	Endpoints/Estimands
PK/PD/Immunogenicity	
To characterize the PK/PD and immunogenicity of ravulizumab in adult participants with DM	• Serum ravulizumab concentrations over the study duration • Change in serum free and total C5 concentrations over the study duration • Incidence and titer of ADAs over the study duration
Safety	
To characterize the overall safety of ravulizumab in participants with DM	• Incidence of TEAEs, TESAEs, and TEAEs leading to study intervention discontinuation

[a] ACR/EULAR-TIS

Abbreviations: ACR/EULAR = American College of Rheumatology/European League Against Rheumatism; ADA = antidrug antibody; C5 = complement component 5; CDASI = Cutaneous Dermatomyositis Disease Area and Severity Index; DM = dermatomyositis; CDA-IGA = Cutaneous Dermatomyositis Activity Physician's Global Assessment; HAQ = health assessment questionnaire; IMACS-TIS = International Myositis Assessment and Clinical Studies-Total Improvement Score; MDAAT = Myositis Disease Activity Assessment Tool; MMT-8 = manual muscle testing subset of 8 muscles; PD = pharmacodynamic(s); PK = pharmacokinetic(s); RCP = Randomized Controlled Period; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; TIS20 = TIS value ≥ 20-point improvement response on IMACS-TIS; TIS40 = TIS value ≥ 40-point improvement response on IMACS-TIS; TIS60 = TIS value ≥ 60-point improvement response on IMACS-TIS

Overall Design

Study ALXN1210-DM-310 is an operationally seamless Phase 2/3, double-blind, randomized, placebo-controlled, parallel group, multicenter study to evaluate the efficacy, safety, PK, PD, and immunogenicity of ravulizumab IV administered q8w (regular dose) in adult participants with DM.

There will be 3 periods in both Part A (Phase 2) and Part B (Phase 3) of this study: Screening Period, Randomized Controlled Period, and Open-Label Extension (OLE) Period. Participants will be screened for eligibility for up to 6 weeks during the Screening Period. Upon completing the last assessment of the Randomized Controlled Period at Week 26 (Part A) or Week 50 (Part B), participants may have the option of continuing into the OLE Period. During the OLE Period, participants in the ravulizumab group will continue to receive ravulizumab treatment, and participants in the placebo group will switch to receive ravulizumab. The study will remain double-blinded during the OLE Period until after data from the Randomized Controlled Period of the study have been cleaned, locked, and unblinded.

The primary efficacy endpoint may be assessed in an interim analysis (Part A) (see Section 9.5.1). If the futility criterion is met, the Sponsor may stop further enrollment in the study or discontinue the study, after recommendation from an Independent Data Monitoring Committee (IDMC). Part B will not be initiated if Part A results in futility or is terminated due to safety concerns. Another interim analysis may be conducted in Part B for sample-size estimation.

Randomized Controlled Period

All participants randomized into the study are expected to complete the Randomized Controlled Period and will be followed until the end of the Randomized Controlled Period.

Participants who discontinue study intervention will complete the Randomized Controlled Period (see Section 7.1). Participants that require acute therapy with standard DM treatment (see Section 6.5.3) due to protocol defined Clinical Worsening and complete all remaining visits of the Randomized Controlled Period (see Section 4.1.3) will be permitted to enter OLE Period.

Participants who discontinue/withdraw consent during the Randomized Controlled Period will not be permitted to enter the OLE Period (see Section 7.2). Participants who will not enter the OLE Period will not receive an infusion at Week 26 (Part A) or Week 50 (Part B).

OLE Period

All participants completing the OLE Period (130 weeks for Part A or 74 weeks for Part B) will have an End of Study (EOS) Visit at Week 156 (Part A) or Week 124 (Part B) and a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention to collect information on concomitant medications, non-pharmacologic therapies and procedures, and adverse events (AEs).

Adjustments of 'protocol allowed' DM medications (Section 6.5.1) will be permitted throughout the OLE Period.

Participants who discontinue study intervention are encouraged to complete the visits and assessments of the OLE Period (see Section 7.1).

Participants who discontinue/withdraw from the study will complete an Early Termination (ET) Visit and a follow-up phone call (see Section 7.2).

Participants from Part A (Phase 2) will not be enrolled in Part B of the study (Phase 3).

Disclosure Statement: This is a blinded, parallel group intervention study with 2 treatment arms followed by an OLE Period. Both Part A and Part B follow this design.

Number of Participants: Participants will be screened until enough participants have been enrolled to achieve an estimated total of approximately 36 participants in Part A (24 ravulizumab:12 placebo) and approximately 114 participants in Part B (76 ravulizumab: 38 placebo).

Intervention Groups and Duration: Eligible participants will be enrolled into the study and will be randomized in a 2:1 ratio (Part A) or stratified by cutaneous manifestations CDASI activity score (≤ 14 and > 14) and randomized in a 2:1 ratio (Part B) to receive intravenous (IV) ravulizumab or placebo (Section 6.3.1) within each stratum.

The study intervention dose for each participant will be based on body weight. The dosing regimen for both Parts A and B consists of a loading dose followed by maintenance doses administered every 8 weeks. The maintenance dosing will be initiated 2 weeks after the loading dose is administered.

The Randomized Controlled Period for Part A will be 26 weeks in duration. The Randomized Controlled Period for Part B will be 50 weeks in duration. Participants may continue to receive ravulizumab or for up to 130 weeks (approximately 2.5 years) (Part A) or up to 74 weeks (approximately 1.5 years) (Part B) in the OLE Period, or until ravulizumab is registered or

approved (in accordance with country-specific regulations), or an alternative option for example transition to a rollover study or an early access program is provided, whichever occurs first. The total study treatment duration for Part A will be approximately 3 years and for Part B approximately 2.5 years.

Data Monitoring Committee: This study will use an Independent Data Monitoring Committee (IDMC) to monitor safety and to perform the planned interim analyses of the study.

Ethical Considerations and Benefit-Risk Assessment

This study will be conducted as specified in this protocol and in accordance 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 ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

A thorough benefit-risk assessment has been performed for ravulizumab IV. Measures will be taken to minimize risk to study participants. The potential risks identified in association with ravulizumab IV are justified by the anticipated benefits that may be afforded to participants with DM.

Brief Summary:

Background: The complement pathway is part of the human immune defense against pathogens. However, if the complement pathway is abnormally activated, it may play a role in the development of the autoimmune disease DM, which results in muscle weakness and skin rashes. Ravulizumab is a treatment that blocks complement and therefore may result in improved symptoms in patients with DM.

Study Population: The study will be conducted in 2 parts and will include participants with DM (≥ 18 years) who did not show an adequate response or are intolerant to 1 or more DM treatments: Part A will include approximately 36 participants randomized in a 2:1 ratio (24 ravulizumab:12 placebo), Part B will include approximately 114 participants randomized in a 2:1 ratio (76 ravulizumab: 38 placebo).

Health Measurement/Outcome: The study will evaluate the effects of ravulizumab on patients with IM with International Myositis Assessment and Clinical Studies Total Improvement Score (IMACS-TIS) as the primary endpoint. Furthermore, efficacy and safety of ravulizumab as well as the PK, PD and potential immune responses to ravulizumab will be assessed. The effects of ravulizumab will be compared to a placebo.

Study Intervention and Intervention Form: Ravulizumab and placebo are formulated as a sterile liquid solution and will be administered as IV infusions. The ravulizumab or placebo dose for each participant will be based on body weight.

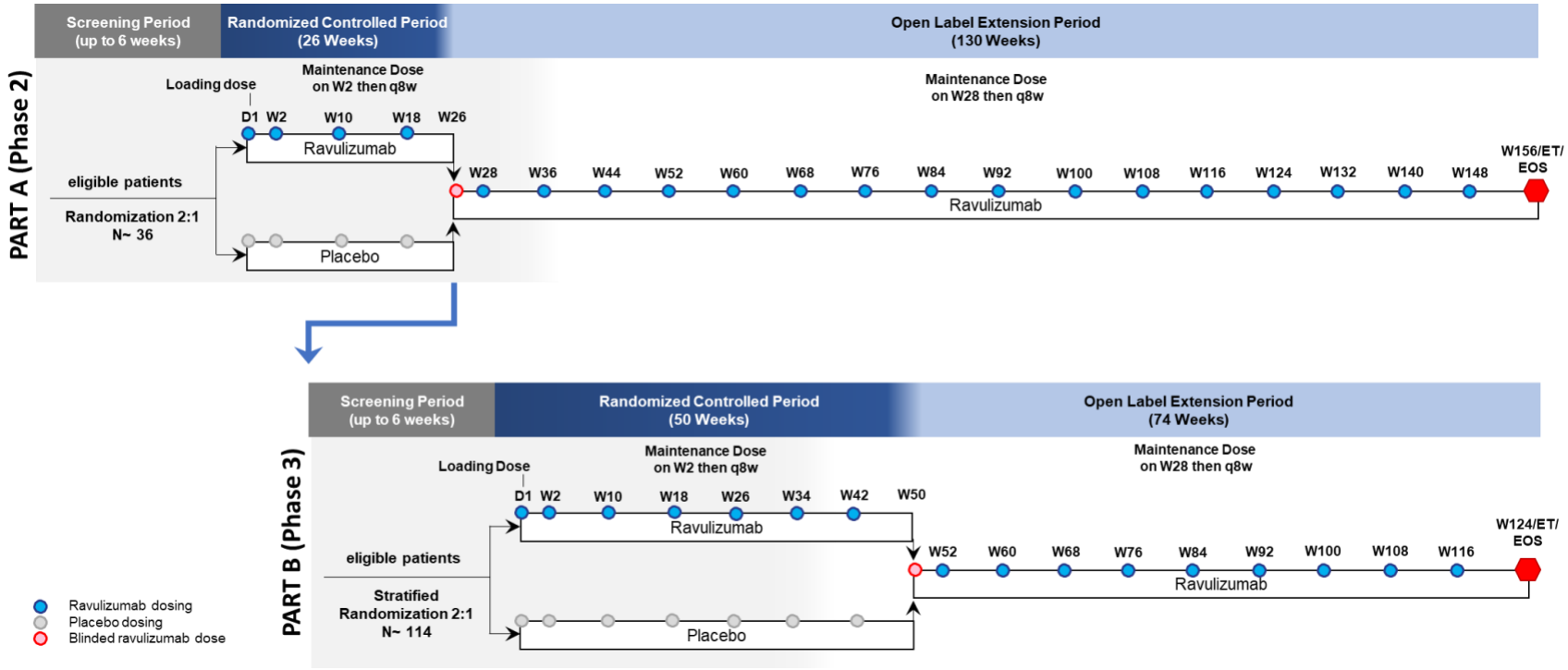
Study/Treatment Duration: Initially a loading dose will be administered. Starting at Week 2 maintenance doses will then be administered every 8 weeks during the 26-week Randomized Controlled Period (RCP) for Part A and 50-week RCP for Part B. Participants will continue to receive ravulizumab during the OLE Period every 8 weeks for up to 130 weeks (Part A) or up to

74 weeks (Part B). The total study treatment duration for Part A and Part B will be approximately 3 years and 2.5 years, respectively.

Visit Frequency: The participant Screening Period covers 42 days before Study Day 1. For Part A, visits will be on Day 1, 15, 71, 127, and 183 during the RCP and on Day 183, 197, 253, 309, 365, 421, 477, 533, 589, 645, 701, 757, 813, 869, 925, 981, 1037, and 1079 during the OLE. For Part B, visits will be on Day 1, 15, 71, 127, 183, 239, 295, and 351 during the RCP and on Day 351, 365, 421, 477, 533, 589, 645, 701, 757, 813, and 869 during the OLE.

1.2. Schema

Figure 1: Study Design Schematic



Abbreviations: D = day; DM = dermatomyositis; EOS = end of study; ET = early termination; N = number of participants; q8w = once every 8 weeks; W = week

1.3. Schedule of Activities

Table 1: Schedule of Activities: Screening Through End of the Randomized Controlled Period for Part A (Phase 2)

Period/Phase	Screening	Randomized Controlled Period					UV	Notes
Study Visit	**1**	**2**	**3**	**4**	**5**	**6/ET**		Participants who discontinue/withdraw from the study should complete the study visit (if at the site for a scheduled visit) or return for an UV as soon as possible within a week and complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details). Participants who will not enter the OLE Period will complete the assessments for Week 26 but not receive an infusion at Week 26 (see Section 6.1.1 for more details).
Study Day	**D-42 to -1**	**D1**	**D15**	**D71**	**D127**	**D183**		
Window (day)			**± 2**	**± 3**	**± 3**	**± 3**		
Weeks	**Up to 6 weeks**		**W2**	**W10**	**W18**	**W26**		
Informed consent	X							
Assessment of inclusion/ exclusion criteria	X							
Medical history	X							
DM history	X							
ACR/EULAR criteria	X							
Weight	X	X	X	X	X	X		
Height	X							
HIV-(1 and 2) testing	X							
Vital signs	X	X	X	X	X	X	X	On dosing days, vital signs will be taken before study intervention administration and after the participant has been resting for at least 5 minutes (see Section 8.2.4).

Table 1: Schedule of Activities: Screening Through End of the Randomized Controlled Period for Part A (Phase 2)

Period/Phase	**Screening**	**Randomized Controlled Period**					**UV**	**Notes**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6/ET**		Participants who discontinue/withdraw from the study should complete the study visit (if at the site for a scheduled visit) or return for an UV as soon as possible within a week and complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details). Participants who will not enter the OLE Period will complete the assessments for Week 26 but not receive an infusion at Week 26 (see Section 6.1.1 for more details).
Study Day	**D-42 to -1**	**D1**	**D15**	**D71**	**D127**	**D183**		
Window (day)			**± 2**	**± 3**	**± 3**	**± 3**		
Weeks	**Up to 6 weeks**		**W2**	**W10**	**W18**	**W26**		
Physical examination	X					X		
Abbreviated physical examination		X	X	X	X		X	To be performed, if necessary, based on the participant's health status and the clinical judgment of the Investigator.
CSMs for IMACS-TIS Determination								
MDAAT	X	X	X	X	X	X	X	MDAAT should be performed before the physician global activity assessment. These are the 6 IMACS core set measures that will be used for IMACS-TIS determination.
Physician global activity assessment	X	X	X	X	X	X	X	
Patient global activity assessment	X	X	X	X	X	X	X	
MMT-8	X	X	X	X	X	X	X	
HAQ	X	X	X	X	X	X	X	
Laboratory tests for muscle enzymes	X	X	X	X	X	X	X	

Table 1: Schedule of Activities: Screening Through End of the Randomized Controlled Period for Part A (Phase 2)

Period/Phase	**Screening**	**Randomized Controlled Period**					**UV**	**Notes**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6/ET**		Participants who discontinue/withdraw from the study should complete the study visit (if at the site for a scheduled visit) or return for an UV as soon as possible within a week and complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details). Participants who will not enter the OLE Period will complete the assessments for Week 26 but not receive an infusion at Week 26 (see Section 6.1.1 for more details).
Study Day	**D-42 to -1**	**D1**	**D15**	**D71**	**D127**	**D183**		
Window (day)			**± 2**	**± 3**	**± 3**	**± 3**		
Weeks	**Up to 6 weeks**		**W2**	**W10**	**W18**	**W26**		
CDASI Activity and Damage	X	X	X	X	X	X		
CDA-IGA	X	X	X	X	X	X		
EQ-5D-5L	X	X	X	X	X	X		
5D-itch scale	X	X	X	X	X	X		
PROMIS-29 v2.1	X	X	X	X	X	X		
SF-36	X	X	X	X	X	X		
FACIT-Fatigue	X	X	X	X	X	X		
DM-DSQ	X	X	X	X	X	X		Participants will complete this assessment once a day starting from Day 1.
ECG	X					X		
30s CST		X				X		
Handheld dynamometry		X				X		

Table 1: Schedule of Activities: Screening Through End of the Randomized Controlled Period for Part A (Phase 2)

Period/Phase	**Screening**	**Randomized Controlled Period**					**UV**	**Notes**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6/ET**		Participants who discontinue/withdraw from the study should complete the study visit (if at the site for a scheduled visit) or return for an UV as soon as possible within a week and complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details). Participants who will not enter the OLE Period will complete the assessments for Week 26 but not receive an infusion at Week 26 (see Section 6.1.1 for more details).
Study Day	**D-42 to -1**	**D1**	**D15**	**D71**	**D127**	**D183**		
Window (day)			**± 2**	**± 3**	**± 3**	**± 3**		
Weeks	**Up to 6 weeks**		**W2**	**W10**	**W18**	**W26**		
Clinical laboratory tests	X	X	X	X	X	X	X	Clinical laboratory tests will be performed at the central laboratory or designated third party laboratory. Coagulation laboratory test to be completed at Screening only.
Urinalysis	X	X	X	X	X	X		
FSH	X							Performed at Screening in selected female participants to confirm postmenopausal status.
Pregnancy test (WOCBP only)	X	X	X	X	X	X	X	Local urine testing will be standard for this study unless serum testing is required by local regulation or ethics committees. Testing will be done at indicated visits and when necessary at Investigator's discretion (Section 8.2.7).

Table 1: Schedule of Activities: Screening Through End of the Randomized Controlled Period for Part A (Phase 2)

Period/Phase	Screening	Randomized Controlled Period					UV	Notes
Study Visit	**1**	**2**	**3**	**4**	**5**	**6/ET**		Participants who discontinue/withdraw from the study should complete the study visit (if at the site for a scheduled visit) or return for an UV as soon as possible within a week and complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details). Participants who will not enter the OLE Period will complete the assessments for Week 26 but not receive an infusion at Week 26 (see Section 6.1.1 for more details).
Study Day	**D-42 to -1**	**D1**	**D15**	**D71**	**D127**	**D183**		
Window (day)			**± 2**	**± 3**	**± 3**	**± 3**		
Weeks	**Up to 6 weeks**		**W2**	**W10**	**W18**	**W26**		
PK/PD		B/P	T/P	T/P	T/P	T	X	Baseline (B) and trough (T) blood samples for PK and PD will be collected predose (within 90 minutes prior to the start of infusion of study intervention). Peak (P) blood samples for PK/PD samples are to be taken within the 60 minutes following completion of study intervention infusion. B and T samples may be drawn through the venous access created for the dose infusion, prior to administration of the dose. The P samples will be drawn from the participant's opposite, non-infused arm. On Day 183 (Week 26), the T sample is considered a Randomized Controlled Period assessment and the P sample is considered an Extension Period assessment. ET or UV PK/PD sample will be collected anytime. All collection times will be recorded in eCRF.

Table 1: Schedule of Activities: Screening Through End of the Randomized Controlled Period for Part A (Phase 2)

Period/Phase	**Screening**	**Randomized Controlled Period**					**UV**	**Notes**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6/ET**		Participants who discontinue/withdraw from the study should complete the study visit (if at the site for a scheduled visit) or return for an UV as soon as possible within a week and complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details). Participants who will not enter the OLE Period will complete the assessments for Week 26 but not receive an infusion at Week 26 (see Section 6.1.1 for more details).
Study Day	**D-42 to -1**	**D1**	**D15**	**D71**	**D127**	**D183**		
Window (day)			**± 2**	**± 3**	**± 3**	**± 3**		
Weeks	**Up to 6 weeks**		**W2**	**W10**	**W18**	**W26**		
ADA		B		T		T	X	Baseline (B) and trough (T) blood samples for ADA will be collected predose (within 90 minutes prior to the start of infusion of study intervention). ET or UV ADA sample will be collected anytime.
Blood sample for biomarkers	X	X	X	X	X	X	X	Blood samples for biomarkers should be collected predose on dosing days. Samples can be collected at any time on non-dosing days. Blood samples for Myositis-specific autoantibodies will be collected on Day 1 and Day 183 or ET.
Neisseria meningitidis vaccination	X							To reduce the risk of meningococcal infection (*N meningitidis*), all participants must be vaccinated against meningococcal infections within 3 years prior to initiating study intervention as per national and local guidelines. Participants must receive the vaccination at least 2 weeks before first study intervention. The sponsor recommends that national and local guidelines for prophylactic antibiotics should also be followed.

Table 1: Schedule of Activities: Screening Through End of the Randomized Controlled Period for Part A (Phase 2)

Period/Phase	**Screening**	**Randomized Controlled Period**					**UV**	**Notes**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6/ET**		Participants who discontinue/withdraw from the study should complete the study visit (if at the site for a scheduled visit) or return for an UV as soon as possible within a week and complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details). Participants who will not enter the OLE Period will complete the assessments for Week 26 but not receive an infusion at Week 26 (see Section 6.1.1 for more details).
Study Day	**D-42 to -1**	**D1**	**D15**	**D71**	**D127**	**D183**		
Window (day)			**± 2**	**± 3**	**± 3**	**± 3**		
Weeks	**Up to 6 weeks**		**W2**	**W10**	**W18**	**W26**		
Participant Safety Card		X	X	X	X	X	X	Participants will be given a Participant Safety Card prior to the first dose of study intervention. At each visit throughout the study, the study staff will ensure that the participant has the Participant Safety Card.
Randomization		X						
Clinical Worsening criteria check			X	X	X	X	X	Clinical Worsening criteria are described in Section 4.1.3. A scheduled visit or UV will occur 4 weeks (± 7 days) later. Clinical Worsening is confirmed if criteria are met on 2 consecutive visits.
Ravulizumab or placebo infusion		X	X	X	X		X	Study intervention will be administered intravenously via infusion after completion of all other tests and procedures, excluding the peak (P) blood sampling for PK/PD. Unscheduled doses should be discussed with the Sponsor or designee.

Table 1: Schedule of Activities: Screening Through End of the Randomized Controlled Period for Part A (Phase 2)

Period/Phase	Screening	Randomized Controlled Period					UV	Notes
Study Visit	**1**	**2**	**3**	**4**	**5**	**6/ET**		Participants who discontinue/withdraw from the study should complete the study visit (if at the site for a scheduled visit) or return for an UV as soon as possible within a week and complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details). Participants who will not enter the OLE Period will complete the assessments for Week 26 but not receive an infusion at Week 26 (see Section 6.1.1 for more details)
Study Day	**D-42 to -1**	**D1**	**D15**	**D71**	**D127**	**D183**		
Window (day)			**± 2**	**± 3**	**± 3**	**± 3**		
Weeks	**Up to 6 weeks**		**W2**	**W10**	**W18**	**W26**		
Concomitant medication	Continuous monitoring							
Non-drug therapy	Continuous monitoring							
Adverse event	Continuous monitoring							

Abbreviations: 30s CST = 30-second Chair Stand Test; ACR/EULAR = American College of Rheumatology/European League Against Rheumatism; ADA = antidrug antibody; AE = adverse event; CDA-IGA = Cutaneous Dermatomyositis Activity Physician's Global Assessment; CDASI = Cutaneous Dermatomyositis Disease Area and Severity Index; CSM = core set measures; D = day; DM = dermatomyositis; DM-DSQ = Dermatomyositis Disease Symptoms Questionnaire; ECG = electrocardiogram; eCRF = electronic case report form; EQ-5D-5L = European Quality of Life Health 5-item questionnaire dimensions 5 level; ET = Early Termination; FACIT = Functional Assessment of Chronic Illness Therapy; FSH = follicle stimulating hormone; HAQ = Health Assessment Questionnaire; HIV = human immunodeficiency virus; IMACS-TIS = International Myositis Assessment and Clinical Studies-Total Improvement Score; MDAAT = Myositis Disease Activity Assessment Tool; MMT-8 = Manual Muscle Testing subset of 8 muscles; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PROMIS = Patient-reported Outcomes Measurement Information System; SF-36 = Short Form Health Survey (36 questions version); UV = Unscheduled Visit; W = week(s); WOCBP = women of childbearing potential

Table 2: Schedule of Activities: Screening Through End of the Randomized Controlled Period for Part B (Phase 3)

Period/Phase	Screening	Randomized Controlled Period								UV	Notes
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9/ET**		Participants who discontinue/withdraw from the study should complete the study visit (if at the site for a scheduled visit) or return for an UV as soon as possible within a week and complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details). Participants who will not enter the OLE Period will complete the assessments for Week 50 but not receive an infusion at Week 50 (see Section 6.1.1 for more details).
Study Day	**D-42 to -1**	**D1**	**D15**	**D71**	**D127**	**D183**	**D239**	**D295**	**D351**		
Window (day)			**± 2**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		
Weeks	**Up to 6 weeks**		**W2**	**W10**	**W18**	**W26**	**W34**	**W42**	**W50**		
Informed consent	X										
Assessment of inclusion/ exclusion criteria	X										
Medical history	X										
DM history	X										
ACR/EULAR criteria	X										
Weight	X	X	X	X	X	X	X	X	X		
Height	X										
HIV-(1 and 2) testing	X										
Vital signs	X	X	X	X	X	X	X	X	X	X	On dosing days, vital signs will be taken before study intervention administration and after the participant has been resting for at least 5 minutes (see Section 8.2.4).

Table 2: Schedule of Activities: Screening Through End of the Randomized Controlled Period for Part B (Phase 3)

Period/Phase	Screening	Randomized Controlled Period								UV	Notes
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9/ET**		Participants who discontinue/withdraw from the study should complete the study visit (if at the site for a scheduled visit) or return for an UV as soon as possible within a week and complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details). Participants who will not enter the OLE Period will complete the assessments for Week 50 but not receive an infusion at Week 50 (see Section 6.1.1 for more details).
Study Day	**D-42 to -1**	**D1**	**D15**	**D71**	**D127**	**D183**	**D239**	**D295**	**D351**		
Window (day)			**± 2**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		
Weeks	**Up to 6 weeks**		**W2**	**W10**	**W18**	**W26**	**W34**	**W42**	**W50**		
Physical examination	X								X		
Abbreviated physical examination		X	X	X	X	X	X	X		X	To be performed, if necessary, based on the participant's health status and the clinical judgment of the Investigator.
CSMs for IMACS-TIS Determination											
MDAAT	X	X	X	X	X	X	X	X	X	X	MDAAT should be performed before the physician global activity assessment. These are the 6 IMACS core set measures that will be used for IMACS-TIS determination.
Physician global activity assessment	X	X	X	X	X	X	X	X	X	X	
Patient global activity assessment	X	X	X	X	X	X	X	X	X	X	
MMT-8	X	X	X	X	X	X	X	X	X	X	
HAQ	X	X	X	X	X	X	X	X	X	X	
Laboratory tests for muscle enzymes	X	X	X	X	X	X	X	X	X	X	

Table 2: Schedule of Activities: Screening Through End of the Randomized Controlled Period for Part B (Phase 3)

Period/Phase	Screening	Randomized Controlled Period								UV	Notes
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9/ET**		Participants who discontinue/withdraw from the study should complete the study visit (if at the site for a scheduled visit) or return for an UV as soon as possible within a week and complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details). Participants who will not enter the OLE Period will complete the assessments for Week 50 but not receive an infusion at Week 50 (see Section 6.1.1 for more details).
Study Day	**D-42 to -1**	**D1**	**D15**	**D71**	**D127**	**D183**	**D239**	**D295**	**D351**		
Window (day)			**± 2**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		
Weeks	**Up to 6 weeks**		**W2**	**W10**	**W18**	**W26**	**W34**	**W42**	**W50**		
CDASI Activity and Damage	X	X	X	X	X	X	X	X	X		
CDA-IGA	X	X	X	X	X	X	X	X	X		
EQ-5D-5L	X	X	X	X	X	X	X	X	X		
5D-itch scale	X	X	X	X	X	X	X	X	X		
PROMIS-29 v2.1	X	X	X	X	X	X	X	X	X		
SF-36	X	X	X	X	X	X	X	X	X		
FACIT-Fatigue	X	X	X	X	X	X	X	X	X		
DM-DSQ	X	X	X	X	X	X	X	X	X		
ECG	X								X		
30s CST		X							X		
Handheld dynamometry		X							X		

Table 2: Schedule of Activities: Screening Through End of the Randomized Controlled Period for Part B (Phase 3)

Period/Phase	Screening	Randomized Controlled Period								UV	Notes
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9/ET**		Participants who discontinue/withdraw from the study should complete the study visit (if at the site for a scheduled visit) or return for an UV as soon as possible within a week and complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details). Participants who will not enter the OLE Period will complete the assessments for Week 50 but not receive an infusion at Week 50 (see Section 6.1.1 for more details).
Study Day	**D-42 to -1**	**D1**	**D15**	**D71**	**D127**	**D183**	**D239**	**D295**	**D351**		
Window (day)			**± 2**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		
Weeks	**Up to 6 weeks**		**W2**	**W10**	**W18**	**W26**	**W34**	**W42**	**W50**		
Clinical laboratory tests	X	X	X	X	X	X	X	X	X	X	Clinical laboratory tests will be performed at the central laboratory or designated third party laboratory. Coagulation laboratory test to be completed at Screening only.
Urinalysis	X	X	X	X	X	X	X	X	X		
FSH	X										Performed at Screening in selected female participants to confirm postmenopausal status.
Pregnancy test (WOCBP only)	X	X	X	X	X	X	X	X	X	X	Local urine testing will be standard for this study unless serum testing is required by local regulation or ethics committees. Testing will be done at indicated visits and when necessary at Investigator's discretion (Section 8.2.7).

Table 2: Schedule of Activities: Screening Through End of the Randomized Controlled Period for Part B (Phase 3)

Period/Phase	Screening	Randomized Controlled Period								UV	Notes
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9/ET**		Participants who discontinue/withdraw from the study should complete the study visit (if at the site for a scheduled visit) or return for an UV as soon as possible within a week and complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details). Participants who will not enter the OLE Period will complete the assessments for Week 50 but not receive an infusion at Week 50 (see Section 6.1.1 for more details).
Study Day	**D-42 to -1**	**D1**	**D15**	**D71**	**D127**	**D183**	**D239**	**D295**	**D351**		
Window (day)			**± 2**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		
Weeks	**Up to 6 weeks**		**W2**	**W10**	**W18**	**W26**	**W34**	**W42**	**W50**		
PK/PD		B/P	T/P	T/P	T/P	T/P	T/P	T/P	T	X	Baseline (B) and trough (T) blood samples for PK and PD will be collected predose (within 90 minutes prior to the start of infusion of study intervention). Peak (P) blood samples for PK/PD samples are to be taken within the 60 minutes following completion of study intervention infusion. B and T samples may be drawn through the venous access created for the dose infusion, prior to administration of the dose. The P samples will be drawn from the participant's opposite, non-infused arm. On Day 351 (Week 50), the T sample is considered a Randomized Controlled Period assessment and the P sample is considered an Extension Period assessment. ET or UV PK/PD sample will be collected anytime. All collection times will be recorded in eCRF.

Table 2: Schedule of Activities: Screening Through End of the Randomized Controlled Period for Part B (Phase 3)

Period/Phase	**Screening**	**Randomized Controlled Period**								**UV**	**Notes**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9/ET**		Participants who discontinue/withdraw from the study should complete the study visit (if at the site for a scheduled visit) or return for an UV as soon as possible within a week and complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details). Participants who will not enter the OLE Period will complete the assessments for Week 50 but not receive an infusion at Week 50 (see Section 6.1.1 for more details).
Study Day	**D-42 to -1**	**D1**	**D15**	**D71**	**D127**	**D183**	**D239**	**D295**	**D351**		
Window (day)			**± 2**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		
Weeks	**Up to 6 weeks**		**W2**	**W10**	**W18**	**W26**	**W34**	**W42**	**W50**		
ADA		B		T					T	X	Baseline (B) and trough (T) blood samples for ADA will be collected predose (within 90 minutes prior to the start of infusion of study intervention). ET or UV ADA sample will be collected anytime.
Blood sample for biomarkers	X	X	X	X	X	X	X	X	X	X	Blood samples for biomarkers should be collected predose on dosing days. Samples can be collected at any time on non-dosing days. Blood samples for Myositis-specific autoantibodies will be collected on Day 1 and Day 351 or ET.
Neisseria meningitidis vaccination	X										To reduce the risk of meningococcal infection (*N meningitidis*), all participants must be vaccinated against meningococcal infections within 3 years prior to initiating study intervention as per national and local guidelines. Participants must receive the vaccination at least 2 weeks before first study intervention. The sponsor recommends that national and local guidelines for prophylactic antibiotics should also be followed.

Table 2: Schedule of Activities: Screening Through End of the Randomized Controlled Period for Part B (Phase 3)

Period/Phase	Screening	Randomized Controlled Period								UV	Notes
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9/ET**		Participants who discontinue/withdraw from the study should complete the study visit (if at the site for a scheduled visit) or return for an UV as soon as possible within a week and complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details). Participants who will not enter the OLE Period will complete the assessments for Week 50 but not receive an infusion at Week 50 (see Section 6.1.1 for more details).
Study Day	**D-42 to -1**	**D1**	**D15**	**D71**	**D127**	**D183**	**D239**	**D295**	**D351**		
Window (day)			**± 2**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		
Weeks	**Up to 6 weeks**		**W2**	**W10**	**W18**	**W26**	**W34**	**W42**	**W50**		
Participant Safety Card		X	X	X	X	X	X	X	X	X	Participants will be given a Participant Safety Card prior to the first dose of study intervention. At each visit throughout the study, the study staff will ensure that the participant has the Participant Safety Card.
Randomization		X									
Clinical Worsening criteria check			X	X	X	X	X	X	X	X	Clinical Worsening criteria are described in Section 4.1.3. A scheduled visit or UV will occur 4 weeks (± 7 days) later. Clinical Worsening is confirmed if criteria are met on ~~two~~ 2 consecutive visits.
Ravulizumab or placebo infusion		X	X	X	X	X	X	X		X	Study intervention will be administered intravenously via infusion after completion of all other tests and procedures, excluding the peak (P) blood sampling for PK/PD. Unscheduled doses should be discussed with the Sponsor or designee.

Table 2: Schedule of Activities: Screening Through End of the Randomized Controlled Period for Part B (Phase 3)

Period/Phase	Screening	Randomized Controlled Period								UV	Notes
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9/ET**		Participants who discontinue/withdraw from the study should complete the study visit (if at the site for a scheduled visit) or return for an UV as soon as possible within a week and complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details). Participants who will not enter the OLE Period will complete the assessments for Week 50 but not receive an infusion at Week 50 (see Section 6.1.1 for more details)
Study Day	**D-42 to -1**	**D1**	**D15**	**D71**	**D127**	**D183**	**D239**	**D295**	**D351**		
Window (day)			**± 2**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		
Weeks	**Up to 6 weeks**		**W2**	**W10**	**W18**	**W26**	**W34**	**W42**	**W50**		
Concomitant medication	Continuous monitoring										
Non-drug therapy	Continuous monitoring										
Adverse event	Continuous monitoring										

Abbreviations: 30s CST = 30-second Chair Stand Test; ACR/EULAR = American College of Rheumatology/European League Against Rheumatism; ADA = antidrug antibody; AE = adverse event; CDA-IGA = Cutaneous Dermatomyositis Activity Physician's Global Assessment; CDASI = Cutaneous Dermatomyositis Disease Area and Severity Index; CSM = core set measures; D = day; DM = dermatomyositis; DM-DSQ = Dermatomyositis Disease Symptoms Questionnaire; ECG = electrocardiogram; eCRF = electronic case report form; EQ-5D-5L = European Quality of Life Health 5-item questionnaire dimensions 5 level; ET = Early Termination; FACIT = Functional Assessment of Chronic Illness Therapy; FSH = follicle stimulating hormone; HAQ = Health Assessment Questionnaire; HIV = human immunodeficiency virus; IMACS-TIS = International Myositis Assessment and Clinical Studies-Total Improvement Score; MDAAT = Myositis Disease Activity Assessment Tool; MMT-8 = Manual Muscle Testing subset of 8 muscles; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PROMIS = Patient-reported Outcomes Measurement Information System; SF-36 = Short Form Health Survey (36 questions version); UV = Unscheduled Visit; W = week(s); WOCBP = women of childbearing potential

Table 3: Schedule of Activities: Open-Label Extension Period for Part A (Phase 2) – Week 26 to Week 100

Period	Open-Label Extension Period											Notes
Visit	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**OLE Period begins at the start of dosing on Day 183** Participants who discontinue/ withdraw from the study should complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details).
Days	**D183**	**D197**	**D253**	**D309**	**D365**	**D421**	**D477**	**D533**	**D589**	**D645**	**D701**	
Weeks	**W26**	**W28**	**W36**	**W44**	**W52**	**W60**	**W68**	**W76**	**W84**	**W92**	**W100**	
Window (day)	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	
Weight		X	X	X	X	X	X	X	X	X	X	
Vital signs		X	X	X	X	X	X	X	X	X	X	On dosing days, vital signs will be taken before study intervention administration and after the participant has been resting for at least 5 minutes (see Section 8.2.4).
Abbreviated physical examination		X	X	X	X	X	X	X	X	X	X	To be performed, if necessary, based on the participant's health status and the clinical judgment of the Investigator.
CSMs for IMACS-TIS Determination												
▪ *MDAAT*		X	X	X	X	X	X	X	X	X	X	MDAAT should be performed before the physician global activity assessment. These are the 6 IMACS core set measures that will be used for IMACS-TIS determination.
▪ *Physician global activity assessment*		X	X	X	X	X	X	X	X	X	X	
▪ *Patient global activity assessment*		X	X	X	X	X	X	X	X	X	X	
▪ *MMT-8*		X	X	X	X	X	X	X	X	X	X	
▪ *HAQ*		X	X	X	X	X	X	X	X	X	X	
▪ *Laboratory tests for muscle enzymes*		X	X	X	X	X	X	X	X	X	X	

Table 3: Schedule of Activities: Open-Label Extension Period for Part A (Phase 2) – Week 26 to Week 100

Period	Open-Label Extension Period											Notes
Visit	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**OLE Period begins at the start of dosing on Day 183** Participants who discontinue/ withdraw from the study should complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details).
Days	**D183**	**D197**	**D253**	**D309**	**D365**	**D421**	**D477**	**D533**	**D589**	**D645**	**D701**	
Weeks	**W26**	**W28**	**W36**	**W44**	**W52**	**W60**	**W68**	**W76**	**W84**	**W92**	**W100**	
Window (day)	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	
CDASI Activity and Damage		X	X	X	X	X	X	X	X	X	X	
CDA-IGA		X	X	X	X	X	X	X	X	X	X	
EQ-5D-5L			X		X	X	X	X	X	X	X	
5D-itch scale			X		X	X	X	X	X	X	X	
PROMIS-29 v2.1		X	X	X	X	X	X	X	X	X	X	
SF-36		X	X	X	X	X	X	X	X	X	X	
FACIT-Fatigue		X	X	X	X	X	X	X	X	X	X	
DM-DSQ		X	X	X	X	X	X	X	X	X	X	
ECG											X	
30s CST			X								X	
Handheld dynamometry				X				X			X	
Clinical laboratory tests		X	X	X	X	X	X	X	X	X	X	Clinical laboratory tests will be performed at the central laboratory or designated third party laboratory.
Urinalysis		X	X	X	X	X	X	X	X	X	X	

Table 3: Schedule of Activities: Open-Label Extension Period for Part A (Phase 2) – Week 26 to Week 100

Period	Open-Label Extension Period											Notes
Visit	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**OLE Period begins at the start of dosing on Day 183** Participants who discontinue/ withdraw from the study should complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details).
Days	**D183**	**D197**	**D253**	**D309**	**D365**	**D421**	**D477**	**D533**	**D589**	**D645**	**D701**	
Weeks	**W26**	**W28**	**W36**	**W44**	**W52**	**W60**	**W68**	**W76**	**W84**	**W92**	**W100**	
Window (day)	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	
Pregnancy test (WOCBP only)		X	X	X	X	X	X	X	X	X	X	Local urine testing will be standard for this study unless serum testing is required by local regulation or ethics committees. Testing will be done at indicated visits and when necessary at Investigator's discretion (Section 8.2.7).
PK/PD	P	T/P	T/P		T/P			T/P			T/P	Trough (T) blood samples for PK and PD will be collected predose (within 90 minutes prior to the start of infusion of study intervention). Peak (P) blood samples for PK/PD are to be taken within the 60 minutes following completion of study intervention infusion. The T samples may be drawn through the venous access created for the dose infusion, prior to administration of the dose. The P samples will be drawn from the participant's opposite, non-infused arm. All collection times will be recorded in the eCRF.
ADA			T		T			T			T	Trough (T) blood samples for ADA will be collected predose (within 90 minutes prior to the start of infusion of study intervention).
Blood sample for biomarkers	X	X	X		X			X			X	Blood samples for biomarkers should be collected predose on dosing days. Samples can be collected at any time on non-dosing days.
Participant Safety Card	X	X	X	X	X	X	X	X	X	X	X	At each visit throughout the study, staff will ensure that the participant has the Participant Safety Card.

Table 3: Schedule of Activities: Open-Label Extension Period for Part A (Phase 2) – Week 26 to Week 100

Period	Open-Label Extension Period											Notes
Visit	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**OLE Period begins at the start of dosing on Day 183** Participants who discontinue/ withdraw from the study should complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details).
Days	**D183**	**D197**	**D253**	**D309**	**D365**	**D421**	**D477**	**D533**	**D589**	**D645**	**D701**	
Weeks	**W26**	**W28**	**W36**	**W44**	**W52**	**W60**	**W68**	**W76**	**W84**	**W92**	**W100**	
Window (day)	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	
Clinical Worsening criteria check		X	X	X	X	X	X	X	X	X	X	Clinical Worsening criteria are described in Section 4.1.3. A scheduled visit or UV will occur 4 weeks (± 7 days) later. Clinical Worsening is confirmed if criteria are met on 2 consecutive visits.
Ravulizumab infusion	X	X	X	X	X	X	X	X	X	X	X	Ravulizumab will be administered intravenously via infusion after completion of all predose tests and procedures. Unscheduled infusions should be discussed with the Medical Monitor or designee.
Concomitant Medication	Continuous monitoring											
Non-drug therapy	Continuous monitoring											
Adverse event	Continuous monitoring											

Abbreviations: 30s CST = 30-second Chair Stand Test; ADA = antidrug antibody; AE = adverse event; CDA-IGA = Cutaneous Dermatomyositis Activity Physician's Global Assessment; CDASI = Cutaneous Dermatomyositis Disease Area and Severity Index; CSM = core set measures; D = day; DM-DSQ = Dermatomyositis Disease Symptoms Questionnaire; ECG = electrocardiogram; eCRF = electronic case report form; EOS = end of study; EQ-5D-5L = European Quality of Life Health 5-item questionnaire dimensions 5 level; ET = Early Termination; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ = Health Assessment Questionnaire; IMACS-TIS = International Myositis Assessment and Clinical Studies-Total Improvement Score; MDAAT = Myositis Disease Activity Assessment Tool; MMT-8 = Manual Muscle Testing subset of 8 muscles; OLE = Open-Label Extension; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PROMIS = Participant-reported Outcomes Measurement Information System; SF-36 = Short Form Health Survey (36 questions version; UV = Unscheduled Visit; W = week(s); WOCBP = women of childbearing potential

Table 4: Schedule of Activities: Open-Label Extension Period for Part A (Phase 2) – Week 108 – Week 156

Period	Open-Label Extension Period							UV	Notes
Visit	**17**	**18**	**19**	**20**	**21**	**22**	**23/ ET/EOS**		**OLE Period begins at the start of dosing on Day 183** Participants who discontinue/withdraw from the study should complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section **7.2** for more details).
Days	**D757**	**D813**	**D869**	**D925**	**D981**	**D1037**	**D1079**		
Weeks	**W108**	**W116**	**W124**	**W132**	**W140**	**W148**	**W156**		
Window (day)	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**		
Weight	X	X	X	X	X	X	X		
Vital signs	X	X	X	X	X	X	X	X	On dosing days, vital signs will be taken before study intervention administration and after the participant has been resting for at least 5 minutes (see Section 8.2.4).
Physical Examination								X	
Abbreviated physical examination	X	X	X	X	X	X	X		To be performed, if necessary, based on the participant's health status and the clinical judgment of the Investigator.
CSMs for IMACS-TIS Determination									
MDAAT	X	X	X	X	X	X	X	X	MDAAT should be performed before the physician global activity assessment. These are the 6 IMACS core set measures that will be used for IMACS-TIS determination.
Physician global activity assessment	X	X	X	X	X	X	X	X	
Patient global activity assessment	X	X	X	X	X	X	X	X	
MMT-8	X	X	X	X	X	X	X	X	
HAQ	X	X	X	X	X	X	X	X	
Laboratory tests for muscle enzymes	X	X	X	X	X	X	X	X	
CDASI Activity and Damage	X	X	X	X	X	X	X	X	

Table 4: Schedule of Activities: Open-Label Extension Period for Part A (Phase 2) – Week 108 – Week 156

Period	Open-Label Extension Period							UV	Notes
Visit	**17**	**18**	**19**	**20**	**21**	**22**	**23/ ET/EOS**		**OLE Period begins at the start of dosing on Day 183** Participants who discontinue/withdraw from the study should complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section **7.2** for more details).
Days	**D757**	**D813**	**D869**	**D925**	**D981**	**D1037**	**D1079**		
Weeks	**W108**	**W116**	**W124**	**W132**	**W140**	**W148**	**W156**		
Window (day)	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**		
EQ-5D-5L	X		X		X		X		
SF-36	X		X		X		X		
DM-DSQ	X	X	X	X	X	X	X	X	
ECG							X	X	
Clinical laboratory tests	X	X	X	X	X	X	X	X	Clinical laboratory tests will be performed at the central laboratory or designated third party laboratory.
Urinalysis	X	X	X	X	X	X	X	X	
Pregnancy test (WOCBP only)	X	X	X	X	X	X	X	X	Local urine testing will be standard for this study unless serum testing is required by local regulation or ethics committees. Testing will be done at indicated visits and when necessary at Investigator's discretion (Section 8.2.7).
PK/PD				T/P			X	X	Trough (T) blood samples for PK and PD will be collected predose (within 90 minutes prior to the start of infusion of study intervention). Peak (P) blood samples for PK/PD are to be taken within the 60 minutes following completion of study intervention infusion. The T samples may be drawn through the venous access created for the dose infusion, prior to administration of the dose. The P samples will be drawn from the participant's opposite, non-infused arm. The Day 1079/ET/EOS, or UV PK/PD sample will be collected anytime. All collection times will be recorded in the eCRF.
ADA				T			X	X	Trough (T) blood samples for ADA will be collected predose (within 90 minutes prior to the start of infusion of study intervention). Day 1079/ET/EOS, or UV ADA sample will be collected anytime.
Participant Safety Card	X	X	X	X	X	X	X	X	At each visit throughout the study, staff will ensure that the participant has the Participant Safety Card.

Table 4: Schedule of Activities: Open-Label Extension Period for Part A (Phase 2) – Week 108 – Week 156

Period	Open-Label Extension Period							UV	Notes
Visit	**17**	**18**	**19**	**20**	**21**	**22**	**23/ ET/EOS**		**OLE Period begins at the start of dosing on Day 183** Participants who discontinue/withdraw from the study should complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section **7.2** for more details).
Days	**D757**	**D813**	**D869**	**D925**	**D981**	**D1037**	**D1079**		
Weeks	**W108**	**W116**	**W124**	**W132**	**W140**	**W148**	**W156**		
Window (day)	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**		
Clinical Worsening criteria check	X	X	X	X	X	X	X	X	Clinical Worsening criteria are described in Section 4.1.3. A scheduled visit or UV will occur 4 weeks (± 7 days) later. Clinical Worsening is confirmed if criteria are met on 2 consecutive visits.
Ravulizumab infusion	X	X	X	X	X	X		X	Ravulizumab will be administered intravenously via infusion after completion of all predose tests and procedures. Unscheduled infusions should be discussed with the Medical Monitor or designee.
Concomitant Medication	Continuous monitoring								
Non-drug therapy	Continuous monitoring								
Adverse event	Continuous monitoring								

Abbreviations: 30s CST = 30-second Chair Stand Test; ADA = antidrug antibody; AE = adverse event; CDA-IGA = Cutaneous Dermatomyositis Activity Physician's Global Assessment; CDASI = Cutaneous Dermatomyositis Disease Area and Severity Index; CSM = core set measures; D = day; DM-DSQ = Dermatomyositis Disease Symptoms Questionnaire; ECG = electrocardiogram; eCRF = electronic case report form; EOS = end of study; EQ-5D-5L = European Quality of Life Health 5-item questionnaire dimensions 5 level; ET = Early Termination; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ = Health Assessment Questionnaire; IMACS-TIS = International Myositis Assessment and Clinical Studies-Total Improvement Score; MDAAT = Myositis Disease Activity Assessment Tool; MMT-8 = Manual Muscle Testing subset of 8 muscles; OLE = Open-Label Extension; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PROMIS = Participant-reported Outcomes Measurement Information System; SF-36 = Short Form Health Survey (36 questions version; UV = Unscheduled Visit; W = week(s); WOCBP = women of childbearing potential

Table 5: Schedule of Activities: Open-Label Extension Period for Part B (Phase 3)

Period	Open-Label Extension Period											UV	Notes
Visit	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19/ET/ EOS**		OLE Period begins at the start of dosing on Day 351. Participants who discontinue/ withdraw from the study should complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details).
Days	**D351**	**D365**	**D421**	**D477**	**D533**	**D589**	**D645**	**D701**	**D757**	**D813**	**D869**		
Weeks	**W50**	**W52**	**W60**	**W68**	**W76**	**W84**	**W92**	**W100**	**W108**	**W116**	**W124**		
Window (day)	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**		
Weight		X	X	X	X	X	X	X	X	X	X		
Vital signs		X	X	X	X	X	X	X	X	X	X	X	On dosing days, vital signs will be taken before study intervention administration and after the participant has been resting for at least 5 minutes (see Section 8.2.4).
Physical examination											X		
Abbreviated physical examination		X	X	X	X	X	X	X	X	X		X	To be performed, if necessary, based on the participant's health status and the clinical judgment of the Investigator.

Table 5: Schedule of Activities: Open-Label Extension Period for Part B (Phase 3)

Period	Open-Label Extension Period											UV	Notes
Visit	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19/ET/ EOS**		OLE Period begins at the start of dosing on Day 351. Participants who discontinue/ withdraw from the study should complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details).
Days	**D351**	**D365**	**D421**	**D477**	**D533**	**D589**	**D645**	**D701**	**D757**	**D813**	**D869**		
Weeks	**W50**	**W52**	**W60**	**W68**	**W76**	**W84**	**W92**	**W100**	**W108**	**W116**	**W124**		
Window (day)	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**		
CSMs for IMACS-TIS Determination													
MDAAT		X	X	X	X	X	X	X	X	X	X	X	MDAAT should be performed before the physician global activity assessment. These are the 6 IMACS core set measures that will be used for IMACS-TIS determination.
Physician global activity assessment		X	X	X	X	X	X	X	X	X	X	X	
Patient global activity assessment		X	X	X	X	X	X	X	X	X	X	X	
MMT-8		X	X	X	X	X	X	X	X	X	X	X	
HAQ		X	X	X	X	X	X	X	X	X	X	X	
Laboratory tests for muscle enzymes		X	X	X	X	X	X	X	X	X	X	X	
CDASI Activity and Damage		X	X	X	X	X	X	X	X	X	X		
CDA-IGA		X	X	X	X	X	X	X	X	X	X		
EQ-5D-5L			X		X	X	X	X	X	X	X		
5D-itch scale			X		X	X	X	X	X	X	X		
PROMIS-29 v2.1		X	X	X	X	X	X	X	X	X	X		

Table 5: Schedule of Activities: Open-Label Extension Period for Part B (Phase 3)

Period	Open-Label Extension Period											UV	Notes
Visit	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19/ET/ EOS**		OLE Period begins at the start of dosing on Day 351. Participants who discontinue/ withdraw from the study should complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details).
Days	**D351**	**D365**	**D421**	**D477**	**D533**	**D589**	**D645**	**D701**	**D757**	**D813**	**D869**		
Weeks	**W50**	**W52**	**W60**	**W68**	**W76**	**W84**	**W92**	**W100**	**W108**	**W116**	**W124**		
Window (day)	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**		
SF-36		X	X	X	X	X	X	X	X	X	X		
FACIT-Fatigue		X	X	X	X	X	X	X	X	X	X		
DM-DSQ		X	X	X	X	X	X	X	X	X	X		
ECG											X		
30s CST			X								X		
Handheld dynamometry				X				X			X		
Clinical laboratory tests		X	X	X	X	X	X	X	X	X	X	X	Clinical laboratory tests will be performed at the central laboratory or designated third party laboratory.
Urinalysis		X	X	X	X	X	X	X	X	X	X		
Pregnancy test (WOCBP only)		X	X	X	X	X	X	X	X	X	X	X	Local urine testing will be standard for this study unless serum testing is required by local regulation or ethics committees. Testing will be done at indicated visits and when necessary at Investigator's discretion (Section 8.2.7).

Table 5: Schedule of Activities: Open-Label Extension Period for Part B (Phase 3)

Period	Open-Label Extension Period											UV	Notes
Visit	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19/ET/ EOS**		OLE Period begins at the start of dosing on Day 351. Participants who discontinue/ withdraw from the study should complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details).
Days	**D351**	**D365**	**D421**	**D477**	**D533**	**D589**	**D645**	**D701**	**D757**	**D813**	**D869**		
Weeks	**W50**	**W52**	**W60**	**W68**	**W76**	**W84**	**W92**	**W100**	**W108**	**W116**	**W124**		
Window (day)	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**		
PK/PD	P	T/P	T/P		T/P			T/P			X	X	Trough (T) blood samples for PK and PD will be collected predose (within 90 minutes prior to the start of infusion of study intervention). Peak (P) blood samples for PK/PD are to be taken within the 60 minutes following completion of study intervention infusion. The T samples may be drawn through the venous access created for the dose infusion, prior to administration of the dose. The P samples will be drawn from the participant's opposite, non-infused arm. The Day 869/ET/EOS, or UV PK/PD sample will be collected anytime. All collection times will be recorded in the eCRF.

Table 5: Schedule of Activities: Open-Label Extension Period for Part B (Phase 3)

Period	Open-Label Extension Period											UV	Notes
Visit	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19/ET/ EOS**		OLE Period begins at the start of dosing on Day 351. Participants who discontinue/ withdraw from the study should complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details).
Days	**D351**	**D365**	**D421**	**D477**	**D533**	**D589**	**D645**	**D701**	**D757**	**D813**	**D869**		
Weeks	**W50**	**W52**	**W60**	**W68**	**W76**	**W84**	**W92**	**W100**	**W108**	**W116**	**W124**		
Window (day)	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**		
ADA			T		T			T			X	X	Trough (T) blood samples for ADA will be collected predose (within 90 minutes prior to the start of infusion of study intervention). Day 869/ET/EOS, or UV ADA sample will be collected anytime.
Blood sample for biomarkers	X	X	X		X			X			X	X	Blood samples for biomarkers should be collected predose on dosing days. Samples can be collected at any time on non-dosing days. Blood samples for Myositis-specific autoantibodies will be collected on Day 869 (contingent on first 2 tests).
Participant Safety Card	X	X	X	X	X	X	X	X	X	X	X	X	At each visit throughout the study, staff will ensure that the participant has the Participant Safety Card.
Clinical Worsening criteria check		X	X	X	X	X	X	X	X	X	X	X	Clinical Worsening criteria are described in Section 4.1.3. A scheduled visit or UV will occur 4 weeks (± 7 days) later. Clinical Worsening is confirmed if criteria are met on 2 consecutive visits.

Table 5: Schedule of Activities: Open-Label Extension Period for Part B (Phase 3)

Period	Open-Label Extension Period											UV	Notes
Visit	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19/ET/ EOS**		OLE Period begins at the start of dosing on Day 351. Participants who discontinue/ withdraw from the study should complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs (see Section 7.2 for more details).
Days	**D351**	**D365**	**D421**	**D477**	**D533**	**D589**	**D645**	**D701**	**D757**	**D813**	**D869**		
Weeks	**W50**	**W52**	**W60**	**W68**	**W76**	**W84**	**W92**	**W100**	**W108**	**W116**	**W124**		
Window (day)	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**		
Ravulizumab infusion	X	X	X	X	X	X	X	X	X	X		X	Ravulizumab will be administered intravenously via infusion after completion of all predose tests and procedures. Unscheduled infusions should be discussed with the Medical Monitor or designee.
Concomitant Medication	Continuous monitoring												
Non-drug therapy	Continuous monitoring												
Adverse event	Continuous monitoring												

Abbreviations: 30s CST = 30-second Chair Stand Test; ADA = antidrug antibody; AE = adverse event; CDA-IGA = Cutaneous Dermatomyositis Activity Physician's Global Assessment; CDASI = Cutaneous Dermatomyositis Disease Area and Severity Index; CSM = core set measures; D = day; DM-DSQ = Dermatomyositis Disease Symptoms Questionnaire; ECG = electrocardiogram; eCRF = electronic case report form; EOS = end of study; EQ-5D-5L = European Quality of Life Health 5-item questionnaire dimensions 5 level; ET = Early Termination; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ = Health Assessment Questionnaire; IMACS-TIS = International Myositis Assessment and Clinical Studies-Total Improvement Score; MDAAT = Myositis Disease Activity Assessment Tool; MMT-8 = Manual Muscle Testing subset of 8 muscles; OLE = Open-Label Extension; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PROMIS = Participant-reported Outcomes Measurement Information System; SF-36 = Short Form Health Survey (36 questions version; UV = Unscheduled Visit; W = week(s); WOCBP = women of childbearing potential

2. INTRODUCTION

2.1. Study Rationale

Complement-mediated injury has been implicated in the pathology of DM as detailed in Section 2.2.1. Muscle biopsies from patients with DM reveal the presence of MAC on the endothelial cells of the endomysial capillaries (Dalakas, 2020; Kissel, 1986) indicating the involvement of C5 in DM and providing the therapeutic rationale for C5 inhibitor therapy.

Immediate, complete, and sustained inhibition of terminal complement activation is efficacious in delivering clinically meaningful outcomes in patients with neuromyelitis optica spectrum disorder (NMOSD) or gMG, where neuroinflammation in the brain and spinal cord or neuromuscular junction, respectively, is considered an important cause of the neurodegeneration that underlies the pathology of these diseases. This has been demonstrated by eculizumab (SOLIRIS®), a C5 inhibitor approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with NMOSD (Pittock, 2019) and gMG (Howard, 2017; Muppidi, 2019).

Ravulizumab is a recombinant, humanized mAb with high specificity against human C5 and blocks the cleavage of C5 into the pro-inflammatory C5a and the pro-inflammatory and lytic C5b-9. Ravulizumab was engineered by introducing 4 targeted amino acid changes into the sequence of the heavy chain of eculizumab, the first generation C5 inhibitor. These sequence modifications have resulted in an increased serum elimination half-life of ravulizumab compared to eculizumab, enabling an extended dosing interval.

Ravulizumab has been shown to achieve immediate, complete, and sustained terminal complement inhibition in patients with PNH, in patients with aHUS, and in adult patients with generalized gMG (gMG), and it is currently being developed as a treatment in several other complement-related indications. It is expected that the same dosing regimen approved for PNH, aHUS, and gMG will also achieve comparable levels of complement inhibition in patients with DM. The combination of clinically relevant outcomes with terminal complement inhibition in other complement-mediated diseases and PD effects of ravulizumab on terminal complement provide the rationale for the hypothesis that ravulizumab may improve the clinical manifestations of DM in patients, and in particular, lead to a reduction in muscle weakness and cutaneous manifestations.

The primary objective of this study is to investigate the efficacy, safety, PK, PD, and immunogenicity of ravulizumab in adult participants with DM. To achieve this objective, this study will be conducted in 2 parts:

1. Part A (Phase 2) will evaluate the safety, efficacy, PK, PD, and immunogenicity of ravulizumab in adult participants with DM to provide initial evidence of efficacy.
2. Part B (Phase 3) will confirm efficacy, safety, PK, PD, and immunogenicity of ravulizumab in adult participants with DM.

2.2. Dermatomyositis Background

DM is an autoimmune idiopathic inflammatory disease characterized by distinct skin rashes and muscle weakness (Bendewald, 2010; Bohan, 1975; Dalakas, 2015; Isak, 2018; Mahil, 2012). Patients with DM typically present with proximal muscle weakness and cutaneous manifestations that develop over weeks to months (Selva-O'Callaghan, 2018). DM affects both children (juvenile DM) and adults, and women more than men (Dalakas, 2003). In the US, the incidence of DM has been estimated as 1.1 per 100000 person-years (Kronzer, 2021), with a bimodal distribution peaking between the ages of 5 to 15 years and 50 to 60 years (Dalakas, 2015; Dalakas, 2003). Patients with DM generally develop a slow weakening of muscles that make everyday tasks like buttoning or holding objects, combing their hair, rising from a chair, climbing steps, or lifting objects difficult (Dalakas, 2015; (Dalakas, 2003).

Organ systems, such as vascular, pulmonary, gastrointestinal, and cardiac may be involved, with rare cases of interstitial lung disease potentially being fatal (Ernste, 2013). Adult patients with DM have a 9% to 32% increased risk of cancer during the first 3 to 5 years after DM diagnosis (Dalakas, 2015). The most common cancers in women with DM are breast and ovarian cancers; whereas, lung and prostate cancers are the most common in men with DM (Ernste, 2013).

Currently, approved DM treatments are limited (Isak, 2018). Management of DM consists of glucocorticoids alone or in combination with immunosuppressive/immunomodulatory therapies (ISTs), including rituximab and IV immunoglobulin (IVIg) (Dalakas, 2015). Long-term use of glucocorticoids can lead to deleterious complications such as osteoporosis, compression fractures, and avascular necrosis, and use of ISTs can increase the risk of serious infections and are associated with tolerability issues as well as hepatotoxicity (Chandra, 2020; Ernste, 2013). Furthermore, despite therapy, about a third of patients with DM are left with mild to severe disability (Dalakas, 2003) and half of patients considered to be stable do not return to previous levels of work (Marie, 2001). With available therapies, 5-year mortality has been reduced, but is still approximately 25% (Rider, 2011a).

In summary, as there are currently a limited number of treatment options available for patients with DM, many clinical treatment decisions are made empirically and without adequate clinical data. Therefore, there still exists a high unmet medical need for efficacious and safe treatment options for this disease.

2.2.1. Abnormal Complement Activation in DM Pathogenesis

Chronic activation of the immune system by environmental risk factors in individuals with a genetic predisposition is thought to be the underlying cause of DM (Rider, 2011a). Environmental exposures, including streptococcus, echovirus, human growth hormone, interferon α, interferon γ, bovine collagen implants, physical exertion, and ultraviolet radiation, have been implicated in the development of DM. Genetic risk factors associated with susceptibility of individuals to DM include gene polymorphisms known to regulate late responses to environmental agents (eg, polymorphisms of human leukocyte antigen [HLA], and cytokine and immunoglobulin genes).

The pathogenesis of DM is thought to be triggered when autoantibodies directed against the endothelium of endomysial capillaries activate complement component 3 (C3) (Dalakas, 2003) leading to complement-mediated injury against endothelial cells in the muscle (Dalakas, 2003;

Mahil, 2012), as well as MAC deposition in skin and muscle tissue (Magro, 1997). This hypothesis is supported by activation of the complement system as an early disease manifestation of DM (Pinal-Fernandez, 2015).

The complement pathways (classical, alternative, and lectin) all converge at C3. Activation of the terminal complement cascade is initiated by proximal complement-mediated deposition of C5 convertase, which activates C5 by cleaving it to produce C5a and C5b (Matis, 1995); ravulizumab robustly blocks this activation. C5a is one of the strongest chemoattractants and pro-inflammatory modulators (Sallum, 2006), recruiting B and T cells, macrophages and other immune cells to the inflammation site. These inappropriately activated immune cells release cytokines, which further potentiate the abnormal immune response with autoantibody formation and further tissue damage. In DM, activated complement C5a has been shown to up-regulate adhesion molecule expression after binding to endothelial cells, which may lead to cytokine induction (Sallum, 2006).

C5b participates in the formation of the terminal complement (C5b-9) MAC (Tegla, 2011). The MACs are deposited on capillaries and induce perivascular inflammation in muscle fibers (Dalakas, 2015; Dalakas, 2003). The MAC in DM causes necrosis, reduction of the density of endomysial capillaries, ischemia, and muscle fiber destruction (Dalakas, 2015; Pinal-Fernandez, 2015). Microscopic lesions in muscle fibers lead to reduced blood flow and perifascicular atrophy (Dalakas, 2015), which is a highly specific feature of muscle biopsies in patients with DM (specificity > 90%) (Suarez-Calvet, 2017).

These data strongly indicate that abnormal complement activation is central to the pathogenesis of DM.

2.3. Benefit/Risk Assessment

The safety profile for ravulizumab is well established. It has been well tolerated and no unexpected safety concerns have been identified based on all currently available data from clinical development programs as well as post-marketing experience. Ravulizumab functions by blocking terminal complement; therefore, patients have increased susceptibility to serious infections, in particular *Neisseria meningitidis* (refer to Ravulizumab Investigator's Brochure [IB]). Specific risk mitigation measures available to support the safe use of ravulizumab are described in Table 6.

As with any therapeutic protein, there is potential for immunogenicity with administration of ravulizumab. Assessment of immunogenicity will be performed through the duration of the study, as described in Section 8.8. Management of potential hypersensitivity, anaphylaxis and serious infusion reactions is described in Section 10.1.

2.3.1. Risk Assessment

Table 6: Ravulizumab Identified and Potential Risks

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Identified risk		
Meningococcal infection	Complement C5 inhibition is known to increase the susceptibility to infections caused by *Neisseria meningitidis*.	Participants must be vaccinated against all available serotypes of *N meningitidis* (A, C, Y, W 135, and B) per the inclusion criteria and Schedule of Activities. Participants must receive the vaccination at least 2 weeks before first study intervention. Each participant will be provided with a Participant Safety Card with signs and symptoms of meningococcal infection, instructions on when to contact a healthcare provider, and relevant contact information. The Participant Safety Card will be checked at each visit (Schedule of Activities, Section 1.3).
Potential risk		
Serious infection	Because participants with dermatomyositis (DM) may be immunosuppressed due to concomitant steroid and immunosuppressive/immunomodulatory therapy (IST) use, an increased risk of serious infections among these participants may occur. Apart from the predictable risk of infection with *Neisseria* species, which is well-known and directly related to its mechanism of action, the mechanism which might lead to other serious infections remains unclear.	Increased awareness of healthcare professionals and participants about the potential risk of serious infection. Monitoring for signs and symptoms of serious infections will be conducted as part of the safety assessments for this study.
Immunogenicity	Treatment with any therapeutic protein has the potential to induce an immune response. Potential clinical consequences may include severe hypersensitivity type reactions, decrease in efficacy and potential risk of causing local (infusion site) and systemic (infusion-related) reactions (Casadevall, 2002; Li, 2001).	Stop infusion in the event of any drug-related adverse events like systemic hypersensitivity or anaphylaxis. Monitoring for hypersensitivity and infusion-related reactions will be conducted as part of safety assessments for this study (Section 10.1).

Table 6: Ravulizumab Identified and Potential Risks

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Only 2 patients have been identified with treatment-emergent ADA across ravulizumab clinical studies in all indications tested to date. There was no association or impact of immunogenicity on PK, safety, or efficacy in either of these patients.	
Pregnancy exposure/lactation	No studies of ravulizumab have been conducted in pregnant or breastfeeding women. There are no data available on excretion of ravulizumab in breast milk.	Pregnant or nursing female participants will be excluded from this clinical study. Women and men enrolled in the study, and their spouses/partners, must use a highly effective or acceptable method of contraception during treatment and for a period of 8 months following the final dose of study intervention. Breastfeeding should be discontinued during treatment and up to 8 months after treatment with ravulizumab (Section 10.5).

2.3.1.1. Coronavirus Disease 2019

The coronavirus disease 2019 (COVID-19) pandemic is active in many countries at the time of this protocol. Given this unique circumstance, specific consideration has been given to the risks and benefits of the study as they relate to COVID-19 (Section 10.8) and vaccination against the disease (see Section 10.9).

2.3.2. Benefit Assessment

DM is a debilitating multi-systemic disease centered around cutaneous manifestations, and muscle weakness and pain. Current therapies fail to provide meaningful benefit in a substantial number of patients; thus, discovery of new therapies is important to address this unmet medical need. Clinical research provides a pragmatic approach to identify effective treatments to reduce disease burden. Although efficacy of ravulizumab has not been previously studied in participants with DM, it represents an appropriate candidate for investigation due to its plausible mechanism of action in DM. The scientific and therapeutic hypothesis for the potential benefit in DM is discussed in Section 2.2.1. Of important note, ravulizumab has been found to be safe and well-tolerated in other indications.

2.3.3. Overall Benefit: Risk Conclusion

Given the measures taken to minimize risk to participants in this study, the potential risks identified in association with ravulizumab are justified by the anticipated benefits that may be afforded to participants with DM.

3. OBJECTIVES AND ESTIMANDS AND/OR ENDPOINTS

Table 7: Mapping Objectives to Endpoints for Part A (Phase 2 Portion)

Objectives	Endpoints/Estimands
Primary	
To determine the effect of ravulizumab compared with placebo in the treatment of DM based on improvement in Total Improvement Score (TIS) IMAC-TIS[a]	IMACS-TIS[a] (TIS40) response at Week 26 of the Randomized Controlled Period as per defined composite estimand (see Section 3.1)
Secondary	
To assess the efficacy of ravulizumab compared with placebo in the treatment of DM based on improvement in efficacy endpoints	• TIS at Week 26 • Change from baseline in CDASI Activity Score at Week 26 • Change from baseline in 5 IMACS core set measures (extra-muscular disease activity based on MDAAT, physician global activity assessment, patient global activity assessment, MMT-8, HAQ) at Week 26 • Response related to muscle enzymes: - normalization of most abnormal baseline enzyme at Week 26 • CDASI response (7-point improvement) at Week 26 • CDA-IGA response (almost clear or clear) at Week 26 • TIS20 response at Week 26 • TIS60 response at Week 26 • Time to First Response of TIS20, TIS40, or TIS60 respectively • Clinical worsening during RCP at 2 consecutive visits • Receipt of acute therapy with standard DM treatment
PK/PD/Immunogenicity	
To characterize the PK/PD and immunogenicity of ravulizumab in adult participants with DM	• Serum ravulizumab concentrations over the study duration • Change in serum free and total C5 concentrations over the study duration • Incidence and titer of ADAs over the study duration

Table 7: Mapping Objectives to Endpoints for Part A (Phase 2 Portion)

Objectives	Endpoints/Estimands
Safety	
To characterize the overall safety of ravulizumab in participants with DM	• Incidence of TEAEs, TESAEs, and TEAEs leading to study intervention discontinuation
Exploratory	
To evaluate the effect of ravulizumab on overall health-related quality of life (HR-QoL) and participant-centered and participant-reported outcomes in DM	• Change from baseline in EQ-5D-5L at Week 26 • Change from baseline in PROMIS-29 v2.1 domains at Week 26 • Change from baseline in SF-36 at Week 26 • Change from baseline of DM symptoms captured in DM-DSQ at Week 26 • Change from baseline of Patient Self-Assessment of Disease Activity (last question in the DM-DSQ) at Week 26
To evaluate, complement, inflammatory, autoimmune, and other soluble biomarkers in adult participants with DM	• Presence of myositis-specific autoantibodies (eg, anti-MDA5, anti-NXP2/MJ, and anti-synthetase/Jo-1, anti-TIF1) in blood, and change from baseline in specific autoantibody/autoantibodies titer over the course of the study • Change from baseline in plasma complement activation (eg, sC5b-9, etc) over the course of the study • Change from baseline in serum inflammatory markers (eg, IL6, etc) and other soluble markers (eg, KL6, etc) over the course of the study
To assess the efficacy of ravulizumab in the treatment of DM based on other efficacy endpoints	• Change from baseline using scale to measure pruritus (5D-itch scale) at Week 26 • Incidence of protocol-defined Clinical Worsening during RCP • Change from baseline in handheld dynamometry performance at Week 26 • Change from baseline in 30-second Chair Stand Test (30s CST) at Week 26 • Change from baseline in FACIT-Fatigue at Week 26

Table 7: Mapping Objectives to Endpoints for Part A (Phase 2 Portion)

[a] ACR/EULAR-TIS

Abbreviations: ACR/EULAR = American College of Rheumatology/European League Against Rheumatism; ADA = antidrug antibody; anti-MDA5 = antimelanoma differentiation-associated protein 5; anti-NXP2/MJ = antinuclear matrix protein 2; anti-TIF1= anti-transcription intermediary factor 1; C5 = complement component 5; CDA-IGA = Cutaneous Dermatomyositis Activity Physician's Global Assessment; CDASI = Cutaneous Dermatomyositis Disease Area and Severity Index; DM = dermatomyositis; DM-DSQ = dermatomyositis disease symptoms questionnaire; EQ-5D-5L = European Quality of Life Health 5-item questionnaire dimensions 5 level; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ = health assessment questionnaire; IMACS-TIS = International Myositis Assessment and Clinical Studies-Total Improvement Score; IL6 = interleukin 6; MDAAT = Myositis Disease Activity Assessment Tool; MMT-8 = manual muscle testing subset of 8 muscles; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PROMIS = Patient-Reported Outcomes Measurement Information System; RCP = Randomized Controlled Period; sC5b-9 = soluble terminal complement complex; SF-36 = Short Form Health Survey (36 questions version); TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; TIS20 = ≥ 20-point improvement response on IMACS-TIS; TIS40 = ≥ 40-point improvement response on IMACS-TIS; TIS60 = ≥ 60-point improvement response on IMACS-TIS

Table 8: Mapping Objectives to Endpoints/Estimands for Part B (Phase 3 Portion)

Objectives	Endpoints/Estimands
Primary	
To determine the effect of ravulizumab compared with placebo in the treatment of DM based on improvement in Total Improvement Score (TIS) IMAC-TIS[a]	IMACS-TIS[a] (TIS40) response at Week 50 of the Randomized Controlled Period as per defined composite estimand (see Section 3.1)
Key Secondary	
To assess the efficacy of ravulizumab compared with placebo in the treatment of DM based on improvement in components of IMACS and other myositis activity measures	• TIS at Week 50 • Change from baseline in MMT-8 at Week 50 • Change from baseline in extra-muscular disease activity based on MDAAT at Week 50 • Change from baseline in CDASI Activity Score at Week 50
Secondary	
To assess the efficacy of ravulizumab compared with placebo in the treatment of DM based on other efficacy endpoints	• Change from baseline in 3 IMACS core set measurements (physician global activity score, patient global activity score, HAQ) at Week 50 • Response related to muscle enzymes: - normalization of most abnormal baseline enzyme at Week 50 • CDASI response (7-point improvement from baseline) at Week 50 • CDA-IGA response (almost clear or clear) at Week 50 • TIS20 response at Week 50 • TIS60 response at Week 50 • Time to First Response of TIS20, TIS40, or TIS60, respectively • Clinical worsening during RCP at 2 consecutive visits • Receipt of acute therapy with standard DM treatment

Table 8: Mapping Objectives to Endpoints/Estimands for Part B (Phase 3 Portion)

Objectives	Endpoints/Estimands
PK/PD/Immunogenicity	
To characterize the PK/PD and immunogenicity of ravulizumab in adult participants with DM	• Serum ravulizumab concentration over the study duration • Change in serum free and total C5 concentrations over the study duration • Incidence and titer of ADAs over the study duration
Safety	
To characterize the overall safety of ravulizumab in participants with DM	• Incidence of TEAEs, TESAEs, and TEAEs leading to study intervention discontinuation
Exploratory	
To evaluate the effect of ravulizumab compared with placebo on overall health-related quality of life (HR-QoL) and participant-centered and participant-reported outcomes in DM	• Change from baseline in EQ-5D-5L at Week 50 • Change from baseline in PROMIS-29 v2.1 domains at Week 50 • Change from baseline in SF-36 at Week 50 • Change from baseline of DM symptoms captured in DM-DSQ at Week 50 • Change from baseline of Patient Self-Assessment of Disease Activity (last question in the DM-DSQ) at Week 50
To evaluate, complement, inflammatory, autoimmune, and other soluble biomarkers in adult participants with DM	• Presence of myositis-specific autoantibodies (eg, anti-MDA5, anti-NXP2/MJ, and anti-synthetase/Jo-1, anti-TIF1) in blood, and change from baseline in specific autoantibody/autoantibodies titer over the course of the study • Change from baseline in plasma complement activation (eg, sC5b-9, etc) over the course of the study • Change from baseline in serum inflammatory markers (eg, IL6, etc) and other soluble markers (eg, KL6, etc) over the course of the study

Table 8: Mapping Objectives to Endpoints/Estimands for Part B (Phase 3 Portion)

Objectives	Endpoints/Estimands
To assess the efficacy of ravulizumab compared with placebo in the treatment of DM based on other efficacy endpoints	• Change from baseline using scale to measure pruritus (5D-itch scale) at Week 50 • Incidence of protocol-defined Clinical Worsening during RCP • Change from baseline in handheld dynamometry performance at Week 50 • Change from baseline in 30-second Chair Stand Test (30s CST) at Week 50 • Change from baseline in FACIT-Fatigue score at Week 50

[a] ACR/EULAR-TIS

Abbreviations: ACR/EULAR = American College of Rheumatology/European League Against Rheumatism; ADA = antidrug antibody; anti-MDA5 = anti-melanoma differentiation-associated protein 5; anti-NXP2/MJ = antinuclear matrix protein 2; anti-TIF1= anti-transcription intermediary factor 1; C5 = complement component 5; CDA-IGA = Cutaneous Dermatomyositis Activity Physician's Global Assessment; CDASI = Cutaneous Dermatomyositis Disease Area and Severity Index; DM = dermatomyositis; DM-DSQ = dermatomyositis disease symptoms questionnaire; EQ-5D-5L = European Quality of Life Health 5-item questionnaire dimensions 5 level; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ = Health Assessment Questionnaire; IMACS-TIS = International Myositis Assessment and Clinical Studies-Total Improvement Score; IL6 = interleukin 6; MDAAT = Myositis Disease Activity Assessment Tool; MMT-8 = manual muscle testing subset of 8 muscles; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PROMIS = Patient-Reported Outcomes Measurement Information System; RCP = Randomized Controlled Period; sC5b-9 = soluble terminal complement complex; SF-36 = Short Form Health Survey (36 questions version); TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; TIS20 = ≥ 20-point improvement response on IMACS-TIS; TIS40 = ≥ 40-point improvement response on IMACS-TIS; TIS60 = ≥ 60-point improvement response on IMACS-TIS

Table 9: Mapping Objectives to Endpoints/Estimands for Open-Label Extension (Part A and Part B)

Objectives	Endpoints/Estimands
Exploratory	
To evaluate the long-term effect of ravulizumab treatment in participants with DM based on improvement in components of the IMACS	• TIS at Week 156 (Part A) or Week 124 (Part B) • Change from baseline in MMT-8 at Week 156 (Part A) or Week 124 (Part B) • Change from baseline in physician global activity assessment at Week 156 (Part A) or Week 124 (Part B) • Change from baseline in extra-muscular disease activity based on MDAAT at Week 156 (Part A) or Week 124 (Part B) • Change from baseline in HAQ at Week 156 (Part A) or Week 124 (Part B)

Table 9: Mapping Objectives to Endpoints/Estimands for Open-Label Extension (Part A and Part B)

Objectives	Endpoints/Estimands
To evaluate the long-term effect of ravulizumab on overall health-related quality of life (HR-QoL) and participant-centered and participant-reported outcomes in DM	• Change from baseline in EQ-5D-5L at Week 156 (Part A) or Week 124 (Part B) • Change from baseline in PROMIS-29 v2.1 domains at Week 156 (Part A) or Week 124 (Part B) • Change from baseline in SF-36 at Week 156 (Part A) or Week 124 (Part B) • Change from baseline of DM symptoms captured in DM-DSQ at Week 156 (Part A) or Week 124 (Part B) • Change from baseline of Patient Global Assessment of Disease Activity (last question in the DM-DSQ) at Week 156 (Part A) or Week 124 (Part B)
To characterize the long-term safety of ravulizumab in participants with DM	• Incidence of TEAEs, TESAEs, and TEAEs leading to study intervention discontinuation
To characterize the long-term PK/PD and immunogenicity of ravulizumab in adult participants with DM	• Serum ravulizumab concentration at Week 156 (Part A) or Week 124 (Part B) • Change in serum free and total C5 concentrations at Week 156 (Part A) or Week 124 (Part B) • Incidence and titer of ADAs through Week 156 (Part A) or Week 124 (Part B)
To evaluate complement, inflammatory, autoimmune and other soluble biomarkers in adult participants with DM	• Change from baseline (only in subjects positive at baseline) in specific autoantibody (eg, anti-MDA5, anti-NXP2/MJ, and anti-synthetase/Jo-1, anti-TIF-1) titers over the course of the study • Change from baseline in plasma complement activation (eg, sC5b-9, etc) at Week 156 (Part A) or Week 124 (Part B) • Change from baseline in serum inflammatory markers (eg, IL6, etc) and other soluble markers (eg, KL6, etc) over the course of the study

Table 9: Mapping Objectives to Endpoints/Estimands for Open-Label Extension (Part A and Part B)

Objectives	Endpoints/Estimands
To assess the long-term efficacy of ravulizumab in the treatment of DM based on other efficacy endpoints	• Change from baseline using scale to measure pruritus (5D-itch scale) at Week 156 (Part A) or Week 124 (Part B) • Change from baseline in CDASI Activity Score at Week 156 (Part A) or Week 124 (Part B) • CDA-IGA response (almost clear or clear) at Week 156 (Part A) or Week 124 (Part B) • Change from baseline in handheld dynamometry performance at Week 156 (Part A) or Week 124 (Part B) • Change from baseline in 30-second Chair Stand Test (30s CST) at Week 156 (Part A) or Week 124 (Part B) • Change from baseline in FACIT-Fatigue score at Week 156 (Part A) or Week 124 (Part B)
To evaluate the long-term use of DM treatment in participants with DM concurrently receiving ravulizumab	• Percentage of participants steroid-free or minimal maintenance dose of 5 mg (prednisone equivalent) or less at the end of the OLE Period • Cumulative steroid dose from baseline

Abbreviations: ADA = antidrug antibody; anti-MDA5 = antimelanoma differentiation-associated protein 5; anti-NXP2/MJ = antinuclear matrix protein; anti-TIF-1 = anti-transcription intermediary factor 1; C5 = complement component 5; CDA-IGA = Cutaneous Dermatomyositis Activity Physician's Global Assessment; CDASI = Cutaneous Dermatomyositis Disease Area and Severity Index; DM = dermatomyositis; DM-DSQ = dermatomyositis disease symptoms questionnaire; EQ-5D-5L = European Quality of Life Health 5-item questionnaire dimensions 5 level; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ = Health Assessment Questionnaire; IMACS = International Myositis Assessment and Clinical Studies; IL6 = interleukin 6; MDAAT = Myositis Disease Activity Assessment Tool; MMT-8 = manual muscle testing subset of 8 muscles; OLE = Open-Label Extension; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PROMIS = Patient-Reported Outcomes Measurement Information System; sC5b-9 = soluble terminal complement complex; SF-36 = Short Form Health Survey (36 questions version); TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; TIS = Total Improvement Score; Primary Estimand(s)

3.1. Primary Estimand(s)

3.1.1. Primary Estimand for Part A

The five attributes for the primary estimand are described below:

- Treatment: Ravulizumab or placebo with or without the use of stable allowed concomitant DM treatments
- Population: adult DM participants who have an inadequate response or are intolerant to at least 1 DM treatment
- Variable: TIS40 response at Week 26

- Intercurrent Events:
  - Discontinued study intervention due to death, AE, or lack of efficacy during the Randomized Controlled Period.
  - Received acute therapy with standard DM treatment or prohibited medications (Section 6.5.2 and Section 6.5.3).
  - Data handling strategy: Participants will be considered non-responders for TIS40 after experiencing these intercurrent events (composite strategy) regardless of the availability of actual TIS40 responses. All available TIS40 data will be used for participants without these intercurrent events.
- Population-level summary: Difference in the percentage of TIS40 response between ravulizumab and placebo arms

The remaining missing data handling for TIS40 is described in Section 9.4.1.2.2.

3.1.2. Primary Estimand for Part B

The primary estimand for Part B is defined in a similar way as in Section 3.1.1. The variable is TIS40 at Week 50.

3.2. Secondary Estimands

This section is not applicable for this study.

Secondary estimands are not applicable for study Part A. The key secondary estimands for Part B will be defined in the Statistical Analysis Plan (SAP).

3.3. Exploratory Estimands

This section is not applicable for this study.

4. STUDY DESIGN

4.1. Overall Design

Study ALXN1210-DM-310 is a Phase 2/3, double-blind, randomized, placebo-controlled, parallel group, multicenter study to evaluate the efficacy, safety, PK, PD, and immunogenicity of ravulizumab in adult participants with DM. The study will be conducted in 2 parts: Part A (Phase 2) described in Section 4.1.1 and Part B (Phase 3) described in Section 4.1.2.

For the purposes of this protocol, information provided that is applicable to only Part A or Part B is clearly demarcated. Information without a specification as to whether it pertains to either Part A Part B is applicable to both parts.

4.1.1. Part A (Phase 2 Portion)

There will be 3 periods in Part A of this study: Screening Period, Randomized Controlled Period, and OLE Period. Participants will be screened for eligibility for up to 6 weeks during the Screening Period. Approximately 36 eligible participants will be randomized in a 2:1 ratio to receive either weight-based IV infusion of ravulizumab (Table 11) or placebo during the double-blind Randomized Controlled Period. Upon completing the last assessment of the Randomized Controlled Period at Week 26, participants may continue into the OLE Period.

For each participant, the Randomized Controlled Period ends and the OLE Period begins at Week 26 (see Section 6.1.1.1 for details). During the OLE Period, participants in the ravulizumab group will continue to receive ravulizumab treatment, and participants in the placebo group will switch to receive ravulizumab treatment. Participants will receive ravulizumab until ravulizumab is registered or approved (in accordance with country-specific regulations) or for up to 130 weeks (approximately 2.5 years), whichever occurs first.

Randomized Controlled Period

All participants randomized into the study are expected to complete the Randomized Controlled Period and will be followed until the end of the Randomized Controlled Period.

Participants who discontinue study intervention will complete the Randomized Controlled Period (see Section 7.1). Participants that require acute therapy with standard DM treatment (see Section 6.5.3) due to protocol defined Clinical Worsening (see Section 4.1.3) and complete all remaining visits of the Randomized Controlled Period will be permitted to enter OLE Period.

Participants who discontinue/withdraw from the study will not be permitted to enter the OLE Period (see Section 7.2). Participants who will not enter the OLE Period will not receive an infusion at Week 26.

OLE Period

All participants completing the OLE Period will have an EOS Visit at Week 156 and a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs.

Participants who discontinue study intervention are encouraged to complete the visits and assessments of the OLE Period (see Section 7.1).

Adjustments of 'protocol allowed' DM medications (Section 6.5.1) will be permitted throughout the OLE Period (Section 6.5.1).

Participants who discontinue/withdraw from the study will complete an Early Termination (ET) Visit and a follow-up phone call (see Section 7.2).

An interim analysis (Section 9.5) for Part A may be conducted when approximately 67% of participants have completed the Week 26 visit or discontinued prematurely from the Randomized Controlled Period of Part A. The unblinded interim analysis would be performed by an IDMC. Details are provided in the DMC Charter and the Interim Analysis Plan of Part A.

Participants from Part A will not be enrolled in Part B (Phase 3) of the study, and therefore, will not contribute to the formal statistical hypothesis testing of Part B.

4.1.2. Part B (Phase 3 Portion)

There will be 3 periods in Part B of this study: Screening Period, Randomized Controlled Period, and OLE Period. Approximately 114 eligible participants will be stratified by cutaneous manifestations (Cutaneous Dermatomyositis Disease Area and Severity Index [CDASI] Activity Score ≤ 14 and > 14) and randomized 2:1 either to ravulizumab IV infusion or placebo IV infusion (Section 6.3) within each stratum.

For each participant, the Randomized Controlled Period ends and the OLE Period begins at Week 50 (see Section 6.1.1.2 for details). During the OLE Period, participants in the ravulizumab group will continue to receive ravulizumab, and participants in the placebo group will switch to receive ravulizumab. Participants will receive ravulizumab until ravulizumab is registered or approved (in accordance with country-specific regulations) or for up to 74 weeks (approximately 1.5 years), whichever occurs first.

Randomized Controlled Period

All participants randomized into the study are expected to complete the Randomized Controlled Period and will be followed until the end of the Randomized Controlled Period.

Participants who discontinue study intervention will complete the Randomized Controlled Period (see Section 7.1). Participants that require acute therapy with standard DM treatment (see Section 6.5.3) due to protocol defined Clinical Worsening (see Section 4.1.3) and complete all remaining visits of the Randomized Controlled Period will be permitted to enter OLE Period.

Participants who discontinue/withdraw from the study will not be permitted to enter the OLE Period (see Section 7.2). Participants who will not enter the OLE Period will not receive an infusion at Week 50.

OLE Period

All participants completing the OLE Period will have an EOS Visit at Week 124 and a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs.

Participants who discontinue study intervention are encouraged to complete the visits and assessments of the OLE Period (see Section 7.1).

Adjustments of 'protocol allowed' DM medications (Section 6.5.1) will be permitted throughout the OLE Period (Section 6.5.1).

Participants who discontinue/withdraw from the study will complete an ET Visit and a follow-up phone call (see Section 7.2).

One interim analysis is planned for sample-size re-estimation for Part B (Section 9.5). The unblinded interim analysis may be performed by an IDMC. Details would be provided in the DMC Charter and the Interim Analysis Plan for Part B. Treatment allocation during the Randomized Controlled Period will remain blinded to participants, site staff, and Alexion throughout the study. The interim analysis for sample size re-estimation may be conducted when approximately 30% of participants have completed the Week 50 visit or discontinued prematurely from Part B.

4.1.3. Clinical Worsening

Clinical Worsening criteria are one of the following:

a. Physician's global activity visual analog scale (VAS) worsening ≥ 2 cm and manual muscle testing subset of 8 muscles (MMT-8) worsening ≥ 20% compared to baseline
b. Global extra muscular activity worsening ≥ 2 cm on the Myositis Disease Activity Assessment Tool (MDAAT) VAS compared to baseline
c. Any 3 of 5 core set measures (CSMs) (excluding muscle enzymes) worsening by ≥ 30% compared to baseline

Clinical Worsening criteria will be checked at the visits described in Section 1.3.

If Clinical Worsening criteria are met, a scheduled visit or an Unscheduled Visit will occur 4 weeks (± 7 days) later. Clinical Worsening is confirmed if at least one of the criteria are met on 2 consecutive visits. The same criterion does not have to be met at both visits.

If participant meets the Clinical Worsening criteria at 2 consecutive visits, the patient may receive acute therapy with standard DM treatment (see Section 6.5.3) with protocol allowed medication(s) (see Section 6.5.1), discontinue study intervention, complete the Randomized Controlled Period, and will be permitted to enter the OLE Period.

4.1.4. Completion of Treatment

Participants will be considered to have completed the study treatment in the Randomized Controlled Period if they receive the last scheduled blinded dose at Week 18 (Part A) or Week 42 (Part B). All participants who discontinue the study intervention during the Randomized Controlled Period will be followed up for safety and efficacy assessments until the

end of the Randomized Controlled Period, withdrawal of consent, or lost to follow-up, whichever occurs earlier (see Section 7).

Participants will be considered to have completed the study treatment in the OLE Period if they receive the last scheduled dose at Week 148 (Part A) or Week 116 (Part B), the participant terminates the study early, due to termination of the study by Alexion, or the participant transitions to approved product.

4.1.5. Completion of Randomized Controlled Period and OLE Period

Participants will be considered to have completed the Randomized Controlled Period of the study if they complete the last scheduled visit specified in the Schedule of Activities (SoA; see Section 1.3) for this period.

Participants who complete Week 26 (Part A) or Week 50 (Part B) but do not receive a dose at that visit will be considered as discontinued from the study and will not be permitted to enter the OLE Period.

Participants will be considered to have completed the OLE Period of the study if they complete the last scheduled visit specified in the SoA (see Section 1.3), the participant terminates the study early due to termination of the study by Alexion, or the participant transitions to approved product.

4.2. Scientific Rationale for Study Design

4.2.1. Study Population and Treatment Duration

This study focuses on patients with DM who continue to show symptoms after treatment with presently available medications. While approved DM treatments are limited, in practice, a range of immunosuppressive medicines are used to mitigate symptoms of the condition (Chandra, 2020; Ernste, 2013). While the condition in some DM patients is well-controlled, about a third of patients with DM are left with mild to severe disability (Dalakas, 2003) and half of patients considered to be stable do not return to previous levels of work (Marie, 2001). Complement activity is described to be a contributing factor to DM pathogenesis (Pinal-Fernandez, 2015) and ravulizumab, a C5 inhibitor, is expected to suppress complement activity. Thus, ravulizumab has the potential to provide efficacy in patients whose symptoms are not fully controlled by or who are intolerant to at least one DM treatment.

This study will be conducted in 2 parts: Part A (Phase 2) and Part B (Phase 3).

A randomized, double-blind, placebo-controlled study design was selected for both Parts A and B to provide the most robust evidence of the efficacy of the intervention on disease progression and safety. Randomization minimizes the effects of baseline characteristic differences and confounding factors on the study population. The use of a placebo comparator allows for the true treatment effect of the intervention to be established while also allowing for study management, drug administration, and assessments to be conducted similarly between treatment groups, thus minimizing the potential for bias. For Part A and Part B, a 2:1 randomization was chosen. Participants may continue to use allowed DM treatments described in Section 6.5.1.1. To achieve balance between participants receiving ravulizumab and placebo with respect of skin disease

activity, participants in Part B will be stratified by cutaneous manifestations (CDASI Activity Score ≤ 14 and > 14) for randomization.

The Randomized Controlled Period of 26 weeks for Part A is adequate to provide proof of concept data on the safety and efficacy of ravulizumab in participants with DM. The Randomized Controlled Period of 50 weeks in Part B is adequate to demonstrate the safety and efficacy of ravulizumab in patients with DM. Participants in Parts A and B can then participate in the OLE Period. Our central hypothesis is that DM develops because of autoimmune membrane attack complex (MAC) deposition on affected organs (eg, muscle, skin, lungs). MAC deposition has been demonstrated in skin, muscle, and microvessels.

MAC in DM may be activated through an antibody-independent classical pathway mechanism (Lahoria, 2016). Given that ravulizumab immediately suppresses complement activation to levels below detection, it is predicted to mitigate the proximal cause (MAC formation) of pathology in DM.

A study design with potentially 2 interim analyses was chosen. The first interim analysis would be conducted for futility assessment in Part A. The second interim analysis would allow for a sample size re-estimation for Part B. The sample size re-estimation would enable Alexion to adjust the sample size to ensure adequate power in the event that the estimated treatment effect or variability at the interim analysis differs from the initial assumptions.

An OLE Period was chosen to ensure that all participants in this study will have the opportunity to receive active treatment after the completion of the Randomized Controlled Period of the study. This OLE Period also allows for further evaluation of longer-term safety and efficacy of ravulizumab.

4.2.2. Rationale for Primary Endpoint: International Myositis Assessment and Clinical Studies-Total Improvement Score (IMACS-TIS)

Based on clinical instrument development in systemic lupus erythematosus (SLE) in the mid-1980s and over the last 2 decades, a consortium of rheumatologists, neurologists, and dermatologists under the umbrella of the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) developed the International Myositis Assessment and Clinical Studies (IMACS).

Consensus was reached for a conjoint analysis–based continuous model using absolute percentage change in 6 independent CSMs (physician, patient, and extra-muscular global activity, muscle strength, Health Assessment Questionnaire [HAQ], and muscle enzyme levels). A Total Improvement Score (TIS: 0–100), determined by summing scores in each CSM, was based on the improvement and relative weight of each CSM. Clinically meaningful thresholds for improvement were defined as ≥ 20-point improvement response on International Myositis Assessment and Clinical Studies-Total Improvement Score (IMACS-TIS) (TIS20; mild), ≥ 40-point improvement response on IMACS-TIS (TIS40; moderate) and ≥ 60-point improvement response on IMACS-TIS (TIS60; severe) (Aggarwal, 2017).

4.2.3. Rationale for Secondary Endpoints included in the Multiplicity Adjustment for Part B

The key secondary endpoints in Part B of the study will support the efficacy of ravulizumab in muscle strength and skin severity as well as the total improvement in physician's assessment of the disease activity. The following tools/assessments have been validated in the DM population and are considered adequate for the assessment of efficacy.

- IMACS Total Improvement Score (IMACS-TIS)
- MMT-8
- MDAAT
- CDASI

For a description of each of these tools/assessments see Section 8.1.

4.2.4. Participant Input into Design

Five patients with DM provided input through a patient insight group. Patients described their experiences and challenges with clinical studies and shared ideas on how to improve them. Patients in the insight group provided key insights on several topics including study awareness, care coordination between study Investigator and the patient's clinical team, use of digital tools and telemedicine, travel and food reimbursement, childcare, mental health screening, and patient-reported outcome (PRO) questionnaires. Input provided by the patient insight group was incorporated accordingly.

4.3. Justification for Dose

The proposed dosing regimen of ravulizumab in this study is identical to approved weight-based dosing of ravulizumab in treating adult patients with other complement-mediated disorders (PNH, aHUS, and gMG) and is based on targeting immediate, complete and sustained inhibition of terminal complement in patients with DM. Additionally, this same ravulizumab dosing regimen is being or was investigated in several other complement-related conditions.

Complement activation leading to MAC formation on endothelial cells in capillaries is thought to be a contributing factor for DM pathogenesis (Dalakas, 2011; Lahoria, 2016) (Section 2.2.1). Based on this hypothesis and the PK, PD, immunogenicity, efficacy, and safety data generated in multiple ravulizumab development programs, the approved body weight-based dosing regimen for treating adult patients with PNH, aHUS, and gMG has been selected for this study. This ravulizumab dosing regimen is expected to be beneficial in treating participants with DM through achieving immediate, complete, and sustained inhibition of terminal complement activation.

4.4. End of Study Definition

A participant is considered to have completed the study if the participant has completed all periods (Randomized Controlled Period and OLE Period) of the study including the last scheduled procedure shown in the SoA (Section 1.3). The end of the study is defined as the date the last participant completes the last visit shown in the SoA.

Participants may continue to receive ravulizumab or for up to 130 weeks (approximately 2.5 years; Part A) or up to 74 weeks (approximately 1.5 years; Part B) in the OLE Period, or until ravulizumab is registered or approved (in accordance with country-specific regulations), or an alternative option for example transition to a rollover study or an early access program is provided, whichever occurs first.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. 18 years of age or older at the time of signing the informed consent.

Weight

2. Body weight ≥ 30 kg at the time of Screening.

Sex

3. Male or female.

Type of Participant and Disease Characteristics

4. **Diagnosis:** Meet 2017 ACR/EULAR classification criteria for definite or probable DM (Lundberg, 2017).
5. Participants who have an inadequate response or are intolerant to 1 or more DM treatments, including systemic glucocorticoids or ISTs (eg, azathioprine, methotrexate, rituximab, IVIg), either in combination or as monotherapy.
6. Participants under treatment with glucocorticoids and/or ISTs who are on stable therapy as described in Table 14 and who will be able to remain on stable therapy throughout the Randomized Controlled Period.

   OR

   Participants under treatment with glucocorticoids and/or ISTs who complete an appropriate washout period for these treatments before the Day 1 Visit as described in Table 15 (eg, 6-month washout period for rituximab; 3-month washout period for IVIg or subcutaneous immunoglobulin [SCIg]).
7. **Disease severity:** Participants who show disease severity at Screening using the following criteria:
   a. MMT-8 of ≤ 142 (out of a maximum of 150) and 2 additional IMACS CSMs out of 5 at Screening such as:
      - Patient Global Activity assessment of ≥ 2.0 cm on a 10 cm VAS
      - Physician Global Activity assessment of ≥ 2.0 cm on a 10 cm VAS
      - HAQ disability index with ≥ 0.25
      - Elevation of at least one of the muscle enzymes (which includes creatine kinase [CK], aldolase, lactate dehydrogenase [LDH], alanine aminotransferase [ALT], and aspartate aminotransferase [AST]) at ≥ 1.3 times the upper limit of normal (ULN)

- Global extramuscular disease activity score with ≥ 2.0 cm on a 10 cm VAS (this measure is the physician's composite evaluation and is based on assessments of activity scores on the constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, and cardiac scales of the MDAAT)

8. **Disease activity:** Participants must meet one of the following criteria to ensure enrollment of active disease rather than weakness due to muscle damage.
    a. Muscle or skin biopsy with evidence of active pathological findings of DM within the last 6 months prior to or during Screening
    b. Electromyography evidence of active myositis within the last 6 months prior to or during Screening
    c. Magnetic resonance imaging (MRI) muscle evidence of active myositis within the last 6 months prior to or during Screening
    d. At least 1 muscle enzyme (CK, LDH, aldolase, AST, ALT) in the IMACS panel ≥ 2 times ULN at Screening
    e. Active DM skin rash characterized by inflammatory changes (CDASI Activity Score ≥ 7) at Screening
9. Vaccinated against *N meningitidis* within 3 years prior to initiating ravulizumab as per national and local guidelines. Participants must receive the vaccination at least 2 weeks before first study intervention. The sponsor recommends that national and local guidelines for prophylactic antibiotics should also be followed.
10. Participants who have been diagnosed with cancer within the last 3 years need to have appropriate negative cancer screening as per local standard of care within 6 months before Screening (basal or squamous cell skin cancer or carcinoma in situ of the cervix needs to have been excised and without evidence of residual disease for at least 3 months before Screening).

Pregnancy and Contraception

11. Female participants of childbearing potential and male participants must follow specified contraception guidance as described in the protocol.

Informed Consent

12. Capable of giving signed informed consent as described in the protocol, which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and the protocol.

5.2. Exclusion Criteria

Medical Conditions

1. Cancer-associated myositis, defined as the diagnosis of myositis within 2 years of the diagnosis of cancer (except basal or squamous cell skin cancer or carcinoma in situ of the cervix that has been excised and cured for at least 3 months before Screening).
2. Evidence of <u>active</u> malignant disease or malignancies diagnosed within the previous 3 years including hematological malignancies and solid tumors (except basal or

squamous cell skin cancer or carcinoma in situ of the cervix that has been excised and cured for at least 3 months before Screening).

3. Participants with other forms of myositis: Clinical diagnosis of inclusion body myositis, polymyositis, necrotizing myopathy, drug-induced myositis/myopathy, anti-synthetase syndrome without DM, cancer-associated myositis (myositis diagnosed within 2 years either before or after a diagnosis of malignancy except squamous cell cancer of skin, basal cell cancer, or cervical carcinoma in situ), myositis with overlap connective tissue disease such as SLE, rheumatoid arthritis, or systemic sclerosis. Participants with secondary Sjogren's syndrome are allowed.
4. As per Investigator's discretion, participants with significant muscle damage (eg, severe muscle atrophy, end-stage muscle disease, MRI with severe atrophy or fibrofatty replacement).
5. History of *N meningitidis* infection.
6. Human immunodeficiency virus (HIV) infection (evidenced by HIV Type 1 or Type 2 antibody titer).
7. History of unexplained infections.
8. Active systemic bacterial, viral, or fungal infection within 14 days prior to ravulizumab administration.
9. Presence of fever ≥ 38°C (100.4°F) within 7 days prior to study intervention administration on Day 1.
10. History of hypersensitivity to murine proteins or to 1 of the excipients of ravulizumab.
11. As per Investigator's discretion, participants with advanced clinically symptomatic interstitial lung disease that would interfere with the participants ability to complete the trial.
12. Any medical condition (such as, cardiac, pulmonary, renal, oncologic, psychiatric disease, or with a diagnosis of fibromyalgia) that, in the opinion of the Investigator, might interfere with the participant's participation in the trial, poses any added risk for the participant, or confounds the assessment of the participant. This includes participants with severe arthritis with limited range of motion or severe diffuse calcinosis or other condition which will prevent quantitative muscle strength testing.
13. History of drug and/or alcohol abuse (according to Diagnostic and Statistical Manual of Mental Disorders [DSM] 5) within 1 year of Screening Visit that would limit participant participation in the study as determined by the Investigator.

Prior/Concomitant Therapy

14. Participants unwilling or unable to complete an appropriate washout period for any of the prohibited medications listed in Section 6.5.2 before the Day 1 visit.
15. Received ≥ 1 mg/kg/day of prednisone or equivalent within 8 weeks before randomization or is currently on a prednisone or equivalent maintenance dose that is > 20 mg/day.

16. Previously or currently treated with a complement inhibitor.

Prior/Concurrent Clinical Study Experience

17. Participation in any other investigational drug study or exposure to an investigational drug or device within 30 days of Screening or 5 half-lives of the investigational drug, whichever is greater.

Other Exclusions

18. Participants who begin a new muscle strengthening exercise program for myositis (eg, physical therapy) in the last 4 weeks or change their current exercise regimen up to 4 weeks before the Day 1 visit. Participants should not initiate any new exercise program or change their current exercise regimen throughout the randomized phase of the trial.
19. Pregnant, breastfeeding, or intending to conceive during the course of the study.
20. Inability or unwillingness to adhere to the protocol requirements.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

There will be no dietary restrictions as part of this study.

5.3.2. Activity

No new exercise program for myositis (including physical therapy) is allowed from 4 weeks before Day 1 until the last day of the Randomized Controlled Period. If the participant is already involved in an exercise regimen for muscle strengthening, there should be no changes in the regimen from 4 weeks before Day 1 to the last day of the Randomized Controlled Period.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (eg, failed eligibility criteria), and any AEs, including any serious adverse events (SAEs) and any related concomitant medication, occurring during the Screening Period.

Individuals who do not meet the criteria for participation in this study (screen failure) due to a reason that is expected to resolve or has resolved, may be rescreened based on discussion and agreement between the Investigator and Alexion Medical Monitor or designee.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Ravulizumab IV is formulated at 10 mg/mL and 100 mg/mL concentrations with a pH 7.0 and 7.4, respectively. Both formulations are presented as sterile, preservative-free solutions for IV administration and are supplied in single-use vials.

The placebo comparator product is formulated as a sterile, clear to translucent colorless solution (10 mg/mL) or a clear to translucent, colorless to yellow solution (100 mg/mL) with the same buffer components, but without active ingredient.

Details regarding the ravulizumab IV formulation are presented in Table 10.

Table 10: Study Intervention

Study intervention name	**Ravulizumab**	**Placebo**
Dose formulation	Vial	Vial
Physical description	Liquid solution practically free from particles	Liquid solution practically free from particles
Dosage Form	Concentrated sterile, preservative-free aqueous solution in single-use 30 mL vials (10 mg/mL formulation) or single-use 11 mL vials (100 mg/mL formulation)	Sterile, preservative-free aqueous solution in single-use 30 mL vials or 11 mL vials
Unit dose strength(s)	300 mg (10 mg/mL formulation) or 1100 mg (100 mg/mL formulation)	Placebo
Dosage level(s)[a]	Weight-based dosing	Weight-based dosing
Route of administration	IV infusion	IV infusion
Use	Experimental	Placebo comparator
IMP and NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by Alexion or contracted manufacturing organization	Provided centrally by Alexion or contracted manufacturing organization
Packaging and labeling	Ravulizumab will be provided in glass vials and stoppered with a butyl rubber stopper with an aluminum overseal and a flip-off cap. Study intervention will be supplied in kits and labeled as required per country requirement.	Placebo will be provided in glass vials and stoppered with a butyl rubber stopper with an aluminum overseal and a flip-off cap. Placebo will be supplied in kits and labeled as required per country requirement.

Table 10: Study Intervention

[a] Detailed information of study intervention dose administration is provided Table 11, Table 12, and Table 13.
Abbreviations: AxMP = auxiliary medicinal product; IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product

6.1.1. Study Intervention(s) Administered

At the scheduled dosing visits (Section 1.3), study intervention infusion should be performed after all other tests and procedures have been completed, excluding the post-dose blood sampling for PK/PD.

The ravulizumab or placebo dose for each participant will be based on body weight and will be administered as an IV infusion. The dosing regimen consists of an initial loading dose at the beginning of the Randomized Controlled Period and the OLE followed by maintenance dosing initiated 2 weeks after loading dose. The maintenance dosing will be administered q8w during the Randomized Controlled Period and OLE (Table 12 and Table 13).

Refer to Table 11 for a reference chart for weight-based dosing.

Table 11: Weight-based Doses of Ravulizumab

Body Weight Range (kg)[a]	Loading Dose (mg)	Maintenance Dose (mg)
≥ 30 to < 40	1200	2700
≥ 40 to < 60	2400	3000
≥ 60 to < 100	2700	3300
≥ 100	3000	3600

Note: Additional dose preparation instructions are provided in the pharmacy manual.
[a] Dose regimen will be based on the last recorded study visit body weight. If the study intervention is prepared the night before a visit, the weight from the most recent study visit should be used.
Abbreviation: aHUS = atypical hemolytic uremic syndrome; gMG = generalized myasthenia gravis; PNH = paroxysmal nocturnal hemoglobinuria

Table 12: Reference Chart for Weight-based Dosing – Study Part A

Study Period	Dosing	Body Weight (kg)[a]	Ravulizumab Dose (mg)	Ravulizumab Volume (mL)	Placebo Volume (mL)	Diluent (0.9% Sodium Chloride) Volume (mL)	Total Volume (mL)
Ravulizumab Group							
Randomized Controlled (10 mg/mL formulation)	Loading dose (Day 1)	≥ 30 to < 40	1200	120	0	120	240
		≥ 40 to < 60	2400	240	0	240	480
		≥ 60 to < 100	2700	270	0	270	540
		≥ 100	3000	300	0	300	600
	Maintenance dose (Days 15, 71, 127)	≥ 30 to < 40	2700	270	0	270	540
		≥ 40 to < 60	3000	300	0	300	600
		≥ 60 to < 100	3300	330	0	330	660
		≥ 100	3600	360	0	360	720
Open-Label Extension (10 mg/mL formulation)	Blinded dose (Day 183)	≥ 30 to < 40	900	90	30	120	240
		≥ 40 to < 60	900	90	150	240	480
		≥ 60 to < 100	900	90	180	270	540
		≥ 100	900	90	210	300	600
Open-Label Extension (100 mg/mL formulation)	Open-label maintenance dose (Days 197 to 1037, q8w)	≥ 30 to < 40	2700	27	0	27	54
		≥ 40 to < 60	3000	30	0	30	60
		≥ 60 to < 100	3300	33	0	33	66
		≥ 100	3600	36	0	36	72

Table 12: Reference Chart for Weight-based Dosing – Study Part A

Study Period	Dosing	Body Weight (kg)[a]	Ravulizumab Dose (mg)	Ravulizumab Volume (mL)	Placebo Volume (mL)	Diluent (0.9% Sodium Chloride) Volume (mL)	Total Volume (mL)
Placebo Group							
Randomized Controlled (10 mg/mL formulation)	Loading dose (Day 1)	≥ 30 to < 40	0	0	120	120	240
		≥ 40 to < 60	0	0	240	240	480
		≥ 60 to < 100	0	0	270	270	540
		≥ 100	0	0	300	300	600
	Maintenance dose (Days 15, 71, 127)	≥ 30 to < 40	0	0	270	270	540
		≥ 40 to < 60	0	0	300	300	600
		≥ 60 to < 100	0	0	330	330	660
		≥ 100	0	0	360	360	720
Open-Label Extension (10 mg/mL formulation)	Blinded loading dose (Day 183)	≥ 30 to < 40	1200	120	0	120	240
		≥ 40 to < 60	2400	240	0	240	480
		≥ 60 to < 100	2700	270	0	270	540
		≥ 100	3000	300	0	300	600
Open-Label Extension (100 mg/mL formulation)	Open-label maintenance dose (Days 197 to 1037, q8w)	≥ 30 to < 40	2700	27	0	27	54
		≥ 40 to < 60	3000	30	0	30	60
		≥ 60 to < 100	3300	33	0	33	66
		≥ 100	3600	36	0	36	72

[a] Dose regimen will be based on the participant's most recently recorded body weight. Contact the Alexion Medical Monitor or designee if a participant's weight drops below 30 kg during the Randomized Controlled Period or Open-Label Extension Period.

Abbreviation: q8w = every 8 weeks

Table 13: Reference Chart for Weight-based Dosing – Study Part B

Study Period	Dosing	Body Weight (kg)[a]	Ravulizumab Dose (mg)	Ravulizumab Volume (mL)	Placebo Volume (mL)	Diluent (0.9% Sodium Chloride) Volume (mL)	Total Volume (mL)
Ravulizumab Group							
Randomized Controlled (100 mg/mL formulation)	Loading dose (Day 1)	≥ 30 to < 40	1200	12	0	12	24
		≥ 40 to < 60	2400	24	0	24	48
		≥ 60 to < 100	2700	27	0	27	54
		≥ 100	3000	30	0	30	60
	Maintenance dose (Days 15, 71, 127, 183, 239, 295)	≥ 30 to < 40	2700	27	0	27	54
		≥ 40 to < 60	3000	30	0	30	60
		≥ 60 to < 100	3300	33	0	33	66
		≥ 100	3600	36	0	36	72
Open-Label Extension (100 mg/mL formulation)	Blinded dose (Day 351)	≥ 30 to < 40	900	9	3	12	24
		≥ 40 to < 60	900	9	15	24	48
		≥ 60 to < 100	900	9	18	27	54
		≥ 100	900	9	21	30	60
	Open-label maintenance dose (Days 365 to 813, q8w)	≥ 30 to < 40	2700	27	0	27	54
		≥ 40 to < 60	3000	30	0	30	60
		≥ 60 to < 100	3300	33	0	33	66
		≥ 100	3600	36	0	36	72

Table 13: Reference Chart for Weight-based Dosing – Study Part B

Study Period	Dosing	Body Weight (kg)[a]	Ravulizumab Dose (mg)	Ravulizumab Volume (mL)	Placebo Volume (mL)	Diluent (0.9% Sodium Chloride) Volume (mL)	Total Volume (mL)
Placebo Group							
Randomized Controlled (100 mg/mL formulation)	Loading dose (Day 1)	≥ 30 to < 40	0	0	12	12	24
		≥ 40 to < 60	0	0	24	24	48
		≥ 60 to < 100	0	0	27	27	54
		≥ 100	0	0	30	30	60
	Maintenance dose (Days 15, 71, 127, 183, 239, 295)	≥ 30 to < 40	0	0	27	27	54
		≥ 40 to < 60	0	0	30	30	60
		≥ 60 to < 100	0	0	33	33	66
		≥ 100	0	0	36	36	72
Open-Label Extension (100 mg/mL formulation)	Blinded loading dose (Day 351)	≥ 30 to < 40	1200	12	0	12	24
		≥ 40 to < 60	2400	24	0	24	48
		≥ 60 to < 100	2700	27	0	27	54
		≥ 100	3000	30	0	30	60
	Open-label maintenance dose (Days 365 to 813, q8w)	≥ 30 to < 40	2700	27	0	27	54
		≥ 40 to < 60	3000	30	0	30	60
		≥ 60 to < 100	3300	33	0	33	66
		≥ 100	3600	36	0	36	72

[a] Dose regimen will be based on the participant's most recently recorded body weight. Contact the Alexion Medical Monitor or designee if a participant's weight drops below 30 kg during the Randomized Controlled Period or Open-Label Extension Period.

Abbreviation: q8w = every 8 weeks

6.1.1.1. Part A

For each participant in Part A, the entire duration is up to 156 weeks, consisting of a Randomized Controlled Period (26 weeks), and an OLE Period (up to 130 weeks, last scheduled dosing at OLE Week 148).

Randomized Controlled Period

Randomized Controlled Period is a double-blind, randomized, placebo-controlled period. Eligible participants will be randomized 2:1 to receive blinded doses of ravulizumab or placebo starting on Day 1 and ending after assessments on Week 26.

- Participants in the ravulizumab group will receive a blinded loading dose of ravulizumab (10 mg/mL formulation) via IV infusion on Day 1, followed by a blinded maintenance dose at Week 2, Week 10, and Week 18 (Table 12).
- Participants in the placebo group will receive a blinded placebo via IV infusion on Day 1, followed by a blinded placebo at Week 2, Week 10, and Week 18.
- Participants who discontinue study intervention will be followed for key efficacy (Section 8.1) and safety assessments (Section 8.2) until the end of the Randomized Controlled Period, withdrawal of consent, or lost to follow-up, whichever is earlier.

Participants who will not enter the OLE Period will complete the assessments for Week 26 but will not receive an infusion at Week 26.

Open-Label Extension Period

The Randomized Controlled Period will end after all predose assessments have been completed at the Week 26 visit. The OLE Period will begin when participants, that elect to continue treatment, receive the Week 26 study intervention infusion. To maintain the treatment randomization blind of the Randomized Controlled Period, participants in both the placebo group and the ravulizumab group will receive blinded doses of ravulizumab as follows:

- Participants in the placebo group will switch to receive a blinded loading dose of ravulizumab (10 mg/mL formulation) at Week 26 (Table 12).
- Participants in the ravulizumab group will receive a blinded ravulizumab dose (10 mg/mL formulation) of 900 mg at Week 26. The 900 mg dose at Week 26 is chosen to maintain complete C5 inhibition over the 2-week period until the next scheduled maintenance dose.

Starting at Week 28, all participants will receive open-label ravulizumab maintenance doses (100 mg/mL formulation) q8w until the last scheduled dose at Week 148 (Table 12).

6.1.1.2. Part B

For each participant in Part B, the entire duration is up to 124 weeks, consisting of a Randomized Controlled Period (50 weeks), and an OLE Period (up to 74 weeks).

Randomized Controlled Period

Randomized Controlled Period is a double-blind, randomized, placebo-controlled period. Eligible participants will be randomized 2:1 to receive blinded doses of ravulizumab or placebo starting on Day 1 and ending after assessments on Week 50.

- Participants in the ravulizumab group will receive a blinded loading dose of ravulizumab (100 mg/mL formulation) via IV infusion on Day 1, followed by a blinded maintenance dose at Week 2, then q8w through Week 42 (Table 13).
- Participants in the placebo group will receive a blinded placebo via IV infusion on Day 1, followed by a blinded placebo at Week 2, then q8w through Week 42 (Table 13).
- Participants who discontinue study intervention will be followed for key efficacy (Section 8.1) and safety assessments (Section 8.2) until the end of the Randomized Controlled Period, withdrawal of consent, or lost to follow-up, whichever is earlier.

Participants who will not enter the OLE Period will complete the assessments for Week 50 but not receive an infusion at Week 50.

Open-Label Extension Period

The Randomized Controlled Period will end after all predose assessments have been completed at the Week 50 visit. The OLE Period will begin when participants who are permitted to enter and elect to continue treatment receive the Week 50 study intervention infusion. To maintain the treatment randomization blind of the Randomized Controlled Period, participants in both the placebo group and the ravulizumab group will receive blinded doses of ravulizumab as follows:

- Participants in the placebo group will receive a blinded loading dose of ravulizumab (100 mg/mL formulation) at Week 50 (Table 13).
- Participants in the ravulizumab group will receive a blinded ravulizumab dose (100 mg/mL formulation) of 900 mg at Week 50. The 900 mg dose at Week 50 is chosen to maintain complete C5 inhibition over the 2-week period until the next scheduled maintenance dose. This dosing maintains the treatment randomization blind of the Randomized Controlled Period.

Starting at Week 52, all participants will receive open-label ravulizumab maintenance doses (100 mg/mL formulation) q8w (Table 13) until the last scheduled dose at Week 116.

6.2. Preparation/Handling/Storage/Accountability

Upon arrival of the study intervention at the study site, the study intervention kits should be removed from the shipping container and stored in their original cartons under refrigerated conditions at 2°C to 8°C (35°F to 47°F) and protected from light. Study interventions should not be frozen.

Study interventions must be stored in a secure, limited-access storage area with temperature monitored daily.

Infusions of study intervention should be prepared using aseptic technique. Ravulizumab and placebo will be further diluted in a 1:1 ratio with compatible diluent. Ravulizumab and placebo will be filtered with a 0.2 micron filter during infusion.

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive the study intervention and only authorized site staff may supply or administer the study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
    a. This responsibility includes the reporting of any temperature excursions and product complaints to AlexionIMPTE@alexion.com and productcomplaints@alexion.com within 1 business day of awareness. A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety, effectiveness, or performance of a product or clinical study material and/or its packaging components after it is has been released for distribution to an end customer that affects the performance of such product.
    b. The pharmacist or other designated individual will maintain records of study intervention delivered to the study site, the inventory at the study site, the distribution to and use by each participant, and the return of materials to the sponsor for storage or disposal/destruction of materials at the study site. These records may include information such as dates, quantities, batch/serial numbers, expiration dates, in-clinic temperature log, and unique code numbers assigned to the study intervention and study participants.
    c. The Investigator will maintain records that adequately document that the participants were administered the correct study treatment kits and reconcile the products received from the drug dispensing center. Investigational product will not be returned to the sponsor or disposed of until accountability has been fully monitored.
4. Further guidance regarding preparation, handling, storage, and accountability and information for the final disposition of unused study intervention is provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

Participants in Parts A and B will be randomly allocated on Day 1 to one of two treatment groups after the Investigator and Alexion Medical Monitor or designee have verified that they are eligible. Participants will be randomized 2:1 in Part A. For Part B, participants will be stratified

by CDASI Activity Score: ≤ 14 and > 14) and randomized 2:1 to either ravulizumab IV infusion or placebo IV infusion within each stratum. Participants will be centrally randomized using interactive response technology (IRT).

6.3.2. Blinding

Participants, all investigative site personnel, Alexion staff, Alexion designees, and any staff directly associated with the conduct of the study will be blinded to participant treatment assignments. To protect the blind, study Part B requires an unblinded pharmacist and potentially an unblinded study nurse. The blinding will be maintained by using identical study intervention kits and labels for ravulizumab and placebo. The randomization code will be maintained by the IRT provider. Participants who elect to continue treatment after completion of the Randomized Controlled Period enter the OLE Period at the end of the Week 26 (Part A) or Week 50 (Part B) visit after completing all scheduled assessments and before receiving ravulizumab. To maintain blinding to the participant's treatment assignment during the Randomized Controlled Period, participants in the placebo group will receive a blinded loading dose of ravulizumab, and participants in the ravulizumab group will receive a blinded dose of 900 mg. For participants in the ravulizumab group, a blinded ravulizumab dose of 900 mg was chosen to ensure maintenance of complete C5 inhibition until the next scheduled maintenance dose at Week 28 (Part A) or Week 52 (Part B). Blind to previous assignment will be maintained for participants, all investigative site personnel, Alexion staff, Alexion designees, and any staff directly associated with the conduct of the study during the OLE Period until after data from the Randomized Controlled Period of the study have been cleaned, locked, and unblinded. Starting at Week 28 (Part A) or Week 52 (Part B), all participants will begin open-label weight-based ravulizumab maintenance doses q8w. Investigators should avoid unscheduled laboratory tests which could potentially break the blind (eg, complement activity assays such as CH50). Access to exploratory biomarker data should be restricted to the Biomarker Development group and all exploratory biomarker data will be received as masked data for exploratory assessment of matrix and assay performance. All exploratory biomarker data that may potentially unblind patients' randomized treatment assignment will not be reported to blinded study personnel until the study blind is broken.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor before unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, Alexion must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

When unblinding is the result of an AE which is unexpected or related and serious, the blind will be broken for that specific participant only. The blind with regard to treatment allocation for that specific participant will be maintained for all study personnel and those responsible for data analysis and interpretation of results at the conclusion of the study, such as biometrics personnel.

Unblinded information will be accessible to those who need to be involved in the safety reporting to Health Authorities, Independent Ethics Committees (IECs), Institutional Review Boards (IRBs), and/or IDMC.

There may be additional analyses in Part A, which may be generated and reviewed by an unblinded team (independent of the study team).

Participants will remain blinded to the treatment received in the Randomized Controlled Period through the OLE Period and may only be unblinded after the study has been completed.

Any participant whose treatment is unblinded during the Randomized Controlled Period will be discontinued from the study.

6.4. Study Intervention Compliance

The infusion of study intervention into participants will be under the supervision of the Investigator or their designee to ensure that participants receive the appropriate dose at the appropriate time points during the study.

The date and time of each dose administered in the clinic will be recorded in the source documents and case report form (CRF).

The volume (mL) of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

For additional information on study intervention and management, refer to the Pharmacy Manual.

6.5. Concomitant Therapy

Any medication (including over the counter or prescription medicines, vitamins, and/or herbal supplements), vaccine, or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information including dose and frequency

The Alexion Medical Monitor or designee should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Allowed Medicine and Therapy

6.5.1.1. Dermatomyositis Treatment

Participants should not discontinue an effective therapy solely for the purpose of entering the clinical study.

Participants who continue allowed DM treatments as concomitant therapy will be required to have received those treatments for at least the amount of time described in Table 14 before the Day 1 Visit and will be required to remain on the same stable dose during the Randomized

Controlled Period. Maximally allowed stable doses are described in Table 14. In some cases, stable doses of allowed DM treatments may be decreased due to safety and/or tolerability issues. Investigators must contact the Alexion Medical Monitor or designee to discuss possible dose changes before adjusting the participant's allowed DM treatment dose.

During the OLE Period, doses of allowed DM treatments may be changed or discontinued. New allowed DM treatments may be started in the OLE Period. Medications listed in Section 6.5.2 are prohibited during the OLE Period. Any change in medication will be properly documented in the CRF.

Table 14: Allowed Concomitant DM Treatments

Medication	Duration of Stable Dose Before Day 1 Visit	Treatment Duration Required Before Day 1 Visit	Maximally Allowed Stable Dose as Concomitant therapy	Dose Modifications Permitted During Randomized Controlled Period[a]
Azathioprine	4 weeks	12 weeks	2.5 mg/kg daily	None
Cyclosporine	4 weeks	12 weeks	5 mg/kg daily	None
Glucocorticoid	4 weeks	4 weeks	20 mg daily Prednisone equivalent[b]	None
Hydroxychloroquine	4 weeks	12 weeks	400 mg daily	None
Intramuscular glucocorticoids[b,c]	NA	NA	80 mg per dose	Only 2 injections allowed (must be separate days)
Leflunomide	4 weeks	12 weeks	20 mg daily	None
Methotrexate	4 weeks	12 weeks	25 mg/week	None
Mycophenolate mofetil/mycophenolic acid	4 weeks	12 weeks	3000 mg daily	None
Sulfasalazine	4 weeks	12 weeks	3 g daily	None
Tacrolimus	4 weeks	12 weeks	0.2 mg/kg daily	None

[a] Unless medically necessary or due to participant safety reasons.
[b] Prednisone equivalent medications and doses are described in the Study Manual.
[c] Do not administer within 72 hours prior to a study visit.
Abbreviations: DM = dermatomyositis; NA = not applicable

Alternatively, participants may choose to discontinue previous DM treatments before the Day 1 Visit but will be required to complete an appropriate washout period, as described in Table 15.

Table 15: Washout Periods Required Before Day 1 Visit

Medication [a]	Washout
Azathioprine	4 weeks

Table 15: Washout Periods Required Before Day 1 Visit

Medication [a]	**Washout**
Cyclosporine	4 weeks
Glucocorticoid [b]	4 weeks
Hydroxychloroquine	8 weeks
Intramuscular glucocorticoids	4 weeks
Leflunomide	12 weeks
Methotrexate	4 weeks
Mycophenolate mofetil/mycophenolic acid	4 weeks
Sulfasalazine	4 weeks
Tacrolimus	4 weeks

[a] For questions regarding a washout period for previous dermatomyositis treatments not listed please consult the Alexion Medical Monitor or designee.
[b] 8-week washout before randomization if received ≥ 1 mg/kg/day or on a maintenance dose > 20 mg/day

6.5.1.2. Other Allowed Therapies

- Medications listed below may be taken as needed but should not be administered within 72 hours prior to the study visit.
    - Antihistamines
    - Non-steroidal anti-inflammatory drugs (NSAIDs)
    - Acetaminophen
    - Antipruritics

  However, participants taking the medications listed above at a stable dose for at least 4 weeks before Screening are allowed to continue these medications.
- Topical steroid hydrocortisone (1%) may be taken as needed but should not be administered within 72 hours prior to the study visit.
- Vitamin B12, vitamin E, creatine, coenzyme Q10, and biotin supplements are permitted in this study. Participants who take any or all of these supplements should be on a stable dose beginning 14 days prior to the first dose of study intervention and remain on the same stable dose for the duration of the Randomized Controlled Period unless alteration in dose is deemed medically necessary or reviewed with the Alexion Medical Monitor or designee.
- All other vitamins and supplements are permitted in this study. Participants are encouraged to remain on stable dosing for the duration of the Randomized Controlled Period of the study.

6.5.2. Disallowed Medicine and Therapy

The following medications and therapies are prohibited during the study:

- Treatments listed in Table 16. Participants must complete the appropriate washout period for these treatments as listed in Table 13 before the Day 1 Visit.
- Eculizumab or other complement inhibitory agent.
- Any investigational therapy or off-label usage of an approved product other than the allowed medication in this protocol for the treatment of DM during the study (Table 14).

Table 16: Washout Periods Required Before Day 1 for Prohibited Medications

Medication [a]	Washout
Abatacept	12 weeks
Adalimumab	12 weeks
Anakinra	1 week
Corticotropin injection	8 weeks
Cyclophosphamide	12 weeks
Etanercept	4 weeks
Infliximab	8 weeks
IVIg/SCIg	12 weeks
IV glucocorticoids	4 weeks
Ocrelizumab	20 weeks
Rituximab	24 weeks
Tocilizumab	10 weeks
Tofacitinib or other JAK inhibitors	4 weeks

[a] For questions regarding a washout period for previous prohibited dermatomyositis treatments and monoclonal antibodies not listed please consult the Alexion Medical Monitor or designee.
Abbreviations: IVIg = intravenous immunoglobulin; JAK = Janus kinase; SCIg = subcutaneous immunoglobulin

Participants who require prohibited medications at any point during the study will be discontinued from the study intervention.

6.5.3. Acute Therapy with Standard DM Treatment

To allow for sufficient time for the study drug to become effective, it is recommended that participants not receive any acute therapy with standard DM treatment during the first 10 weeks of receiving the study intervention during the Randomized Controlled Period.

Acute therapy with standard DM treatment includes an increased dose of a medication that is currently being taken for DM or the initiation of a new DM treatment (glucocorticoid and/or ISTs).

Participants in the Randomized Controlled Period (Part A and Part B) who receive acute therapy with standard DM treatment with protocol allowed medication (see Section 6.5.1) upon confirmation of Clinical Worsening (see Section 4.1.3) will discontinue study intervention, complete the Randomized Controlled Period, and will be permitted to enter the OLE Period. Participants in the Randomized Controlled Period who receive acute therapy with standard DM treatment for other reasons will discontinue study intervention, complete the Randomized Controlled Period visit assessments, but will not be permitted to enter the OLE Period.

All participants who received acute therapy with standard DM treatment during the Randomized Controlled Period and are permitted to enter the OLE will require a weight-based blinded loading dose at Week 26 (Part A) or Week 50 (Part B) as described in Table 12, Table 13, and Section 6.1.1.

Participants randomized to ravulizumab:

Participants in Part A who discontinue therapy before Week 18 will resume treatment in Week 26 with the weight-based blinded loading dose described in the Placebo Group section of Table 12 (no dose adjustments needed).

Participants in Part A who discontinue therapy after Week 18 will resume treatment in Week 26 with the weight-based blinded dose described in the Ravulizumab Group section of Table 12 (no dose adjustments needed).

Participants in Part B who discontinue therapy before Week 42 will resume treatment in Week 50 with the weight-based blinded loading dose described in the Placebo Group section of Table 13 (no dose adjustments needed).

Participants in Part B who discontinue therapy after Week 42 will resume treatment in Week 50 with the weight-based blinded dose described in the Ravulizumab Group section of Table 13 (no dose adjustments needed).

Participants randomized to placebo:

Participants will resume treatment in Week 26 (Part A) or Week 50 (Part B) with the weight-based blinded loading dose described in the Placebo Group section of Table 12 and Table 13 (no dose adjustments needed).

All participants will then continue to receive the weight based open-label maintenance dose.

OLE Period

Adjustments of protocol allowed DM medications will be permitted throughout the OLE Period.

6.6. Dose Modification

Dose modification is not permitted for this study. However, in the event of a missed or incomplete dose, and with the guidance of the Sponsor, unscheduled doses may be administered in order to limit the risk of losing complete terminal complement inhibition.

In the event of treatment discontinuation during the Randomized Controlled Period modifications to the first dose of the OLE may be required (see Section 6.5.3).

6.7. Intervention After the End of the Study

Participants will receive ravulizumab until ravulizumab is registered or approved (in accordance with country-specific regulations) or for up to 130 weeks (approximately 2.5 years) (Part A) or up to 74 weeks (approximately 1.5 years) (Part B) in the OLE Period, whichever occurs first. Ravulizumab will not be provided to participants after the last scheduled dose (Section 1.3). Participants in the Randomized Controlled Period who discontinue study intervention early and do not agree to continue in the study, will be expected to complete the study visit (if at the site for a scheduled visit) or return for an Unscheduled Visit as soon as possible within a week and an ET Visit 8 weeks after the participant's last dose of study intervention. Participants will be followed via a phone call for an additional 21 weeks (± 1 week) after the last dose of study intervention.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to discontinue study intervention.

Participants in the Randomized Controlled Period who discontinue study intervention but do not withdraw consent will remain in the study and will continue to complete study visits as described in the SoA (Section 1.3).

If the decision to discontinue study intervention for any reason falls outside of a study visit, participants are expected to return for an Unscheduled Visit as soon as possible within a week and complete the remaining scheduled visits for the Randomized Controlled Period.

All participants completing the Randomized Controlled Period and not entering the OLE Period will have a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs.

See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and for any further evaluations that need to be completed.

Participants should be considered for discontinuation of study intervention if any of the following occur:

- Severe uncontrolled infection.
- Serious infusion or hypersensitivity reaction (such as bronchospasm with wheezing or requiring ventilator support or symptomatic hypotension, refer to Section 10.1) or serum sickness-like reactions manifesting 1 to 14 days after drug administration and assessed as related to study drug.
- Grade 3 rash or pruritus unresponsive to appropriate treatment according to local or institutional guidelines and assessed as related to study drug.
- Newly diagnosed cardiac arrythmias refractory to treatment as per local or Institutional guidelines and assessed as related to study intervention.
- Severe unintended weight loss (greater or equal to 20% from baseline) during a 6-month period.
- Pregnancy or planned pregnancy.
- Participant is treated with prohibited medications (Section 6.5.2) or acute therapy with standard DM treatment (Section 6.5.3).
- Alexion or the Investigator deem it necessary for the participant based on a documented safety concern or AE or lack of improvement.
- Clinical Worsening as outlined in Section 4.1.3.

7.2. Participant Discontinuation/Withdrawal from the Study

- All efforts should be made to ensure participants are willing to comply with study participation prior to conducting the screening procedures.
- The study staff should notify Alexion and their site monitor of all study withdrawals as soon as possible. The reason for participant discontinuation must be recorded in the source documents and electronic case report form (eCRF).
- A participant may withdraw from the study at any time at the participant's own request.
- Participants who discontinue/withdraw from the study during the Randomized Controlled Period should complete the study visit (if at the site for a scheduled visit) or return for an Unscheduled Visit as soon as possible within a week and complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs.
- Participants who discontinue/withdraw from study during the Randomized Controlled Period will not be permitted to enter the OLE Period.
- Participants who discontinue/withdraw from the study during the OLE Period should complete the ET Visit 8 weeks after the participant's last dose of study intervention. In addition, a follow-up phone call 21 weeks (± 1 week) after the participant's last dose of study intervention will be performed to collect information on concomitant medications, non-pharmacologic therapies and procedures, and AEs.
- Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, Alexion may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records and communicate to the Sponsor.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant 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 to reschedule the missed visit as soon as possible, 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.

- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.2.9.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with Alexion immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- See Section 10.3 for the list of clinical laboratory tests.

8.1. Efficacy Assessments

All efficacy assessments, not completed by the participants themselves, should preferably be performed by the same study staff member throughout the study.

8.1.1. International Myositis Assessment and Clinical Studies (IMACS) Core Set Measures (CSM)

The IMACS group developed a consensus on outcome measures and definitions of improvement that should be used in clinical trials for DM (Aggarwal, 2017). The CSM are described in the following subsections.

8.1.1.1. Myositis Disease Activity Assessment Tool (MDAAT)

The MDAAT assesses disease activity of extramuscular organ systems and muscle in patients with DM (Section 10.8.1). It is a combined tool that includes the Myositis Disease Activity Assessment VAS (MYOACT) and the Myositis Intention to Treat Activities Index (MITAX). The MITAX assesses specific manifestations in 7 organs/systems: constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, cardiac, and muscle. The MYOACT consist of a 10-cm VAS for each organ system and overall. The MDAAT is administered in-person and completed by the clinician (Rider, 2011b). MDAAT will be completed at the timepoints listed in the SoA (Section 1.3) and should be the first clinician assessed IMACS CSM to be completed.

8.1.1.2. Physician Global Activity Assessment

The physician global activity assessment provides an overall rating of disease activity related to myositis Section 10.8.2). Disease activity is judged by the physician based on all information available at the time of evaluation, including the participant's appearance, medical history,

physical examination, laboratory testing, and prescribed medical therapy. The global disease activity score is recorded on a 10-cm VAS anchored at the end points and the middle (Rider, 2011b). The form also includes a 5-point Likert scale to assess the global disease activity. The physician global activity assessment will be completed at timepoints listed in the SoA (Section 1.3).

8.1.1.3. Patient Global Activity Assessment

The patient global activity assessment provides an overall rating of disease activity related to myositis from the participant's perspective (Section 10.8.3). Participants are asked to consider all of the active inflammation in their own muscles, skin, joints, intestines, heart, lungs, or other parts of the body that can improve with treatment. The patient global disease activity score is recorded on a 10-cm VAS that contains a smiley face at the 0-cm anchor and a sad face at the 10-cm anchor to help participants understand the scale (Rider, 2011b). The patient global activity assessment will be completed at timepoints listed in the SoA (Section 1.3).

8.1.1.4. Manual Muscle Testing 8 Muscles Group (MMT-8)

The purpose of the MMT-8 is to measure muscle strength as part of the physical examination. It includes a subset of 8 muscle groups: neck flexors, deltoids, biceps, wrist, extensors, gluteus maximus and medius, quadriceps, and ankle dorsiflexors (Rider, 2011b). MMT-8 will be administered at timepoints listed in the SoA (Section 1.3).

8.1.1.5. Health Assessment Questionnaire (HAQ)

The HAQ is a brief self-report questionnaire that assesses physical function pertaining to activities of daily living in a variety of domains (Rider, 2011b). In this study, the HAQ Disability Index (Section 10.8.5) will be completed at timepoints listed in the SoA (Section 1.3).

8.1.1.6. Muscle Enzymes

As part of the IMACS CSM, laboratory tests to measure serum activities of muscle-associated enzymes including CK, ALT and AST, LDH, and aldolase will be performed. The most abnormal serum muscle enzyme value at baseline will be used for calculation of the TIS (Aggarwal, 2017). Muscle enzymes will be assessed at the timepoints listed in the SoA (Section 1.3).

8.1.2. Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI)

The CDASI is an instrument that separately measures activity and damage in the skin of DM patients (Section 10.8.6). It is a 1-page instrument that contains 3 activity measures (erythema, scale, and erosion/ulceration) and 2 damage measures (poikiloderma and calcinosis). CDASI is completed by the Clinician or Clinician-Investigator while examining the participant (Rider, 2011b). CDASI will be completed at the timepoints listed in the SoA (Section 1.3).

8.1.3. Cutaneous Dermatomyositis Activity Physician's Global Assessment (CDA-IGA)

The Cutaneous Dermatomyositis Activity Physician's Global Assessment (CDA-IGA) is a scale that was created to measure disease severity in patients with skin disease. It is a 5-point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) with morphologic descriptors for

each score (Section 10.8.7). The CDA-IGA is completed by the Investigator and is used to describe the overall appearance of lesions at a given time point. The CDA-IGA will be completed at the timepoints listed in the SoA (Section 1.3).

8.1.4. EuroQoL 5 Dimensions (EQ-5D-5L)

The European Quality of Life Health 5-item questionnaire dimensions 5 level (EQ-5D-5L) (Section 10.8.8) is a self-assessed, standardized instrument to measure health-related quality of life and has been used in a wide range of health conditions (Schrag, 2000). The EQ-5D-5L consists of 2 pages: the EQ-5D-5L descriptive system and the EQ VAS. The EQ-5D-5L will be completed at time points specified in the SoA (Section 1.3), or if a participant is not able to attend the scheduled onsite visit, EQ-5D-5L can be assessed via a phone call.

8.1.4.1. EQ-5D-5L Descriptive System

The descriptive system is a 5-component scale including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Section 10.8.8). Each level is rated on a scale that describes the degree of problems in that area.

8.1.4.2. EQ Visual Analog Scale

The EQ VAS is an overall health state scale where the participant selects a number between 0 and 100 to describe the condition of their health, with 100 being 'The best health state you can imagine' and 0 being 'The worst health state you can imagine' (Section 10.8.8).

This information can be used as a quantitative measure of health outcome as judged by the individual respondents. Previously published studies by EuroQol Group members showed preliminary evidence of the instrument's feasibility, reliability, and validity.

8.1.5. 5D-Itch Scale

The 5D-itch scale is a multidimensional questionnaire, which includes the following 5 dimensions: degree, duration, direction, disability, and distribution (Section 10.8.9). The 5D-itch scale will be completed by the participant at the timepoints described in the SoA (Section 1.3).

8.1.6. Patient-Reported Outcomes Measurement Information System (PROMIS) 29 v2.1 Tool

The Patient-Reported Outcomes Measurement Information System (PROMIS)-29 v2.1 (Section 10.8.10) profile assesses pain intensity using a single 0-10 numeric rating item and 7 health domains (physical function, fatigue, pain interference, depressive symptoms, anxiety, ability to participate in social roles and activities, and sleep disturbance) using 4 items per domain. PROMIS-29 v2.1 will be completed by the participant at the timepoints described in the SoA (Section 1.3).

8.1.7. Short Form Health Survey (36 Questions Version) (SF-36)

The Short Form Health Survey (36 Questions Version) (SF-36) (Version 2.0) is a 36-item self-report of health-related quality of life (Stewart, 1988; Ware, 1992). It contains 8 subscales measuring different domains of health-related quality of life: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social

functioning, role limitations due to emotional problems, and mental health (Section 10.8.11). The SF-36 will be conducted at Screening and at timepoints specified per SoA (Section 1.3). The 2 summary scores are the physical component summary and the mental component summary. There is no single overall score for the SF-36.

8.1.8. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Scale (Version 4) is a short, 13-item, self-reported, easy to administer tool that measures an individual's level of fatigue during their usual daily activities over the past week (Section 10.8.12). The level of fatigue is measured on a five-point Likert-type scale (0 = not at all fatigued; 1 = a little bit fatigued, 2 = somewhat fatigued, 3 = quite a bit fatigued, and 4 = very much fatigued). All items contribute to the sum score with equal weight. FACIT-Fatigue will be completed at timepoints specified in the SoA (Section 1.3).

8.1.9. Dermatomyositis Disease Symptoms Questionnaire (DM-DSQ)

The Dermatomyositis Disease Symptom Questionnaire (DM-DSQ) is a PRO instrument designed to assess symptoms relevant to the experience of patients with DM in the past 24 hours (Part A, RCP) or in the past 7 days (Part A, OLE Period and Part B RCP and OLE Period) (Section 10.8.13). Each item was generated based on a corresponding concept extracted from published qualitative literature (interviews or focus groups with patients) or from direct patient input (minutes from meeting with patients describing their disease and video testimonials of patients from the Myositis Association). There are symptom questions that are rated according to their severity on a 5-point response scale (None, Mild, Moderate, Severe, and Very severe) and questions about disease activity rated on a 5-point response scale (Not at all active, Mildly active, Moderately active, Very active, Extremely active). While DM-DSQ version 1.1 will be used in the Part A RCP and OLE Period, DM-DSQ version 5.0 will be used in the Part B RCP and OLE Period. The DM-DSQ will be completed at the timepoints specified in the SoA (Section 1.3).

8.1.10. 30-Second Chair Stand Test (30s CST)

The 30s CST is a procedure that assesses proximal muscle function (Agarwal, 2006; Rider, 2018) (Section 10.8.14). During the test a participant is asked to rise from a standard-height chair and to sit down as many times as possible in 30 seconds. The 30s CST will be assessed at the timepoints specified in the SoA (Section 1.3).

8.1.11. Handheld Dynamometry

Handheld dynamometry (Rider, 2018) is a procedure for quantitative strength testing. This testing will be conducted by the Investigator or any designee who has been properly trained for the quantitative muscle strength evaluation. When possible, it is highly recommended that all assessments be performed by the same assessor. Muscle strength testing will be performed on prespecified muscles in the upper and lower extremities bilaterally and the force measurements recorded. Handheld dynamometry will be assessed at timepoints specified in the SoA (Section 1.3).

8.1.12. Home Electronic Patient-Reported Outcomes

For Part A, participants will be asked to complete the following PROs at the frequencies described in Table 1.

- DM-DSQ

The PRO will be completed using an electronic device (eg, iPad). Further details of the selected PROs and the process associated with completing the PROs will be included in a separate electronic PRO (ePRO) Manual.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Vaccine and Antibiotic Prophylaxis

As with any complement C5 inhibition, the use of ravulizumab increases the participant's susceptibility to meningococcal infection (*N meningitidis*). To reduce the risk of meningococcal infection, all participants must be vaccinated against meningococcal infection within the 3 years before initiating study intervention.

- Participants must receive a vaccination at least 2 weeks before first study intervention. Participants must be vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement inhibitors (eg, eculizumab, ravulizumab).
- Vaccines against serotypes A, C, Y, W135, and B, where available, are recommended to prevent common pathogenic meningococcal serotypes.
- Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given according to official guidance and local practice on the appropriate use of antibacterial agents.
- All participants should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics, if necessary.

8.2.2. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the following organs/body systems: skin, head, ears, eyes, nose, throat, neck, lymph nodes, chest, heart, abdomen, extremities, and musculoskeletal.
- An abbreviated physical examination will include, at minimum, a body-system relevant examination based upon Investigator judgment and participant symptoms.
- Examiners should pay special attention to clinical signs related to previous serious illnesses.
- For consistency, all efforts should be made to have the physical examination performed by the same qualified study staff at each study visit.

- Additional physical examinations can be performed as medically indicated during the study at the Investigator's discretion.

8.2.3. Height and Weight

Body weight will be measured in pounds or kilograms. Height will be measured in inches or centimeters (Section 1.3).

8.2.4. Vital Signs

- Temperature (°C or °F), pulse rate, respiratory rate, and systolic and diastolic blood pressure (mm Hg), and pulse oximetry will be assessed (Section 1.3).
- Blood pressure and pulse measurements will be assessed seated with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Ideally, the same arm for each participant should be used for measurements.
- O_2 saturation (%) will be collected using pulse oximetry.

8.2.5. Electrocardiograms

- Single 12-lead electrocardiogram (ECG) will be performed at protocol specified visits in the SoA (Section 1.3) using an ECG machine to obtain heart rate and measures of PR, QRS, QT, and RR intervals.
- Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
- The Investigator, Co-Investigator, or Sub-Investigator will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and determine the clinical significance of the results. These assessments will be recorded in the source documents and the eCRF.

8.2.6. Clinical Safety Laboratory Assessments

- See Section 10.3 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 8 weeks after the final dose of study intervention should be repeated until the values return to normal or baseline or are no longer

considered clinically significant by the Investigator or Alexion Medical Monitor or designee.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and Alexion notified.
- All protocol-required laboratory assessments, as defined in Section 10.3, must be collected in accordance with the laboratory manual and the SoA.
- Laboratory assessments performed at the institution's local laboratory that require a change in participant management or are considered clinically significant by the Investigator must be recorded in the AE/SAE eCRF.

8.2.7. Pregnancy

Pregnancy testing must be performed on all women of childbearing potential (WOCBP) at the time points specified in the SoA (Section 1.3). Pregnancy tests (local urine testing will be standard unless serum testing is required by local regulation or ethic committees may also be performed at any time during the study at the Investigator's discretion.

WOCBP must have a negative pregnancy test (serum if required per country regulations) before study intervention administration.

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until termination of the pregnancy.
- If a pregnancy is reported, the Investigator should inform Alexion within 24 hours of learning of the pregnancy and should follow the procedure outlined in Section 10.5.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs. Pregnancy alone is not considered an AE.
- If a participant becomes pregnant, the study intervention must be immediately discontinued, and Alexion must be notified as per Section 10.5. Each pregnancy will be followed to term and Alexion should be notified regarding the outcome (Section 10.5.3).

8.2.8. Participant Safety Card

Before the first dose of the study intervention, a Participant Safety Card will be provided to participants to carry with them at all times until 5.5 terminal half-lives (8 months) after the final dose of ravulizumab. The card is provided to increase participant awareness of the risk of meningococcal infection and promote quick recognition and disclosure of any potential signs or symptoms of meningococcal infection experienced during the course of the study and to inform participants on what actions must be taken if they are experiencing signs or symptoms of infection.

At each visit throughout the study, the study staff will ensure that the participant has the Participant Safety Card (Section 1.3).

8.3. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.4.

AEs will be reported to the Investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (Section 7).

Procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.4.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the last visit specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to Alexion or the designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.4. The Investigator will submit any updated SAE data to Alexion within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE data after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify Alexion.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.4.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow-up on each participant at subsequent visits/contacts. All SAEs and adverse events of special interest (AESIs; as defined in Section 8.3.5) will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section Section 10.4.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification of an SAE by the Investigator to Alexion is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.
- Suspected unexpected serious adverse reactions (SUSARs) must be reported according to local regulatory requirements and Alexion policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion will review and then file it along with the IB and will notify the Institutional Review Board/Independent Ethics Committee (IRBs/IECs), if appropriate according to local requirements.
  - Under the EU CTR 536/2014, events other than SAEs (eg, unexpected events) that may impact the benefit-risk balance should be reported. See definitions in Section 10.4.5.

8.3.5. Medication Error, Drug Abuse, and Drug Misuse

8.3.5.1. Timelines

If an event of medication error, drug abuse, or drug misuse occurs during the study, then the Investigator or other site personnel will report to Alexion or designee immediately but no later than 24 hours of when they become aware of it.

The full definitions and examples of medication error, drug abuse, and drug misuse can be found in Section 10.5.

8.3.5.2. Medication Error

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for a study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

8.3.5.3. Drug Abuse

Drug abuse is the persistent or sporadic intentional, non-therapeutic excessive use of study intervention for a perceived reward or desired non-therapeutic effect.

8.3.5.4. Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of study intervention for medicinal purposes outside of the authorized product information, or for unauthorized study intervention, outside the intended use as specified in the protocol, including deliberate administration of the product by the wrong route.

8.3.6. Adverse Events of Special Interest

Meningococcal infections will be recorded as AESIs.

8.4. Treatment of Overdose

For this study, any dose of ravulizumab greater than that specified in the protocol will be considered an overdose. If dose cannot be established during the Randomized Controlled Period due to blinding, suspected overdose should be defined by the volume administered.

Overdoses are medication errors that are not considered AEs unless there is an untoward medical occurrence resulting from the overdose.

Alexion does not recommend specific treatment for an overdose.

In the event of an overdose or suspected overdose, the Investigator or treating physician should:

- Capture and forward the event, with or without associated AEs, to Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Overdose Report Form within 24 hours of awareness.
- Contact the Alexion Medical Monitor or designee immediately.
- Closely monitor the participant for any AE/SAE.
- Obtain a plasma sample for PK analysis if requested by the Alexion Medical Monitor or designee (determined on a case-by-case basis).
- For unblinded participants, document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Alexion Medical Monitor or designee based on the clinical evaluation of the participant.

8.5. Pharmacokinetics and Pharmacodynamics

- Blood samples for determination of serum drug concentrations and serum free and total C5 will be collected before and after administration of study intervention at the time points specified in the SoA (Section 1.3) according to applicable regulations.
- Instructions for the collection and handling of biological samples will be provided by Alexion. The actual date and time (24-hour clock time) of each sample will be recorded on the eCRF and the central laboratory requisition form.
- Samples collected for analyses of ravulizumab serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Baseline and trough PK/PD blood samples will be collected at predose, within 90 minutes before administering study intervention at visits specified in the SoA (Section 1.3). The predose blood sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose.
- Post-dose PK/PD blood samples will be collected post-dose, within 60 minutes after completing study intervention infusion. The post-dose blood samples will be drawn from the participant's opposite, non-infused arm.

- PK/PD blood samples collected at the ET/EOS visit and at Unscheduled Visits will be collected at any time.
- In the event of an Unscheduled Visit, a PK/PD blood sample will be collected anytime.
- Additional information on sample collection, including blood volume requirements, is provided in the Laboratory Manual.

Study intervention concentration information that may unblind the study will not be reported to investigative sites or blinded personnel.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Please refer to the Laboratory Study Manual for details on sample collection, including blood volume requirements. Biomarker samples may be analyzed after study completion by the absolute value and change from baseline.

8.7.1. Blood Exploratory Biomarkers

Blood (serum and plasma) samples for biomarker research will be collected from all participants at the time points specified in the SoA (Section 1.3) according to applicable regulations.

Biomarkers to be measured may include, but are not limited to, assessments of the following:

- Complement pathway dysregulation (eg, soluble C5b-9 etc)
- Myositis-specific autoantibodies (eg, antimelanoma differentiation-associated protein 5 [anti-MDA5], antinuclear matrix protein 2 (anti-NXP2/MJ), anti-synthetase/Jo-1, etc)
- Soluble biomarkers including inflammatory and prognostic markers (eg, IL6, KL6, etc)

8.7.2. Additional Biomarker Research

Remaining samples from PK, PD, immunogenicity, and biomarker testing will be stored for additional method developments of assays (eg, prognostics and/or companion diagnostics related to the study intervention target, disease process, pathways associated with disease state, other complement related diseases, and/or mechanism of action of ravulizumab).

Samples will be retained for up to 25 years after termination of the study or other period as per local requirements.

8.8. Immunogenicity Assessments

Antibodies to ravulizumab (ie, ADAs) will be evaluated in serum samples collected predose (90 minutes prior to the start of infusion of study intervention) from all participants according to the SoA (Section 1.3) according to applicable regulations. Additionally, serum samples should also

be collected at the final visit from participants who discontinued the study intervention or were withdrawn from the study. These samples will be tested by Alexion or Alexion's designee.

Serum samples will be screened for antibodies binding to ravulizumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of ravulizumab.

The detection and characterization of antibodies to ravulizumab will be performed using a validated assay method by or under the supervision of Alexion. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored for a maximum duration according to local regulations following the last participant's last visit for the study at a facility selected by Alexion to enable further analysis of immune responses to ravulizumab.

8.9. Health Economics Data and/or Medical Resource Utilization

Information regarding outpatient medical visits and hospitalization will be collected in the eCRF by the Investigator and study-site personnel for all participants throughout the study.

This data may be used to conduct exploratory economic analyses.

8.10. Other Assessments and Procedures

8.10.1. Medical History and DM History and Diagnosis

The Principal Investigator or Sub-Investigator will review the participant's medical history including DM history and diagnosis.

The following will be evaluated and documented at the Screening Visit and/or other visits as specified in the SoA (Section 1.3).

- Date of first diagnosis with DM.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The null hypothesis associated with the primary endpoint is that there is no difference in TIS40 response rates between ravulizumab and placebo at Week 26 (Part A) or Week 50 (Part B). The alternative hypothesis is that the response rates are different.

9.2. Sample Size Determination

9.2.1. Part A

A total number of 36 participants will be randomized into the study with a 2:1 (ravulizumab:placebo) allocation ratio to ensure approximately 80% power to detect a difference (ravulizumab–placebo) of 45% in TIS40 response rates with a 2-sided Type 1 error of 0.2, assuming the placebo response rate of 23% and approximately 20% dropout rate.

The sample size was calculated in PASS2022 using the 2-sample test for the difference of proportions with a pooled estimate of variance for the primary endpoint (TIS40).

9.2.2. Part B

A total number of 114 participants will be randomized into the study with a 2:1 (ravulizumab:placebo) allocation ratio to ensure approximately 90% power to detect a difference (ravulizumab–placebo) of 35% in TIS40 response rate with a 2-sided Type 1 error of 0.05, assuming the placebo TIS40 response rate of 23% and approximately 20% dropout rate. The sample size was calculated in PASS2022 using the 2-sample test for the difference of proportions with a pooled estimate of variance for the primary endpoint (TIS40).

An unblinded sample size re-estimation is planned to possibly increase the sample size to a maximum of 150 participants in Part B. The maximum sample size may be updated once the primary analysis of Part A is completed (Section 9.5).

9.3. Populations for Analyses

The analysis sets are defined in Table 17. Unless otherwise specified, the same definitions will be used for the statistical analyses of Part A and Part B where applicable.

Table 17: Study ALXN1210-DM-310 Analysis Populations

Population	Description
Randomized Set	All randomized participants grouped by randomized treatment group (for reporting disposition, demographics, baseline characteristics and efficacy).
PK Analysis Set (PKAS)	All participants who receive at least 1 dose of study intervention and have at least 1 post-dose PK sample
PD Analysis Set (PDAS)	All participants who receive at least 1 dose of study intervention and who have evaluable free or total C5 data

Table 17: Study ALXN1210-DM-310 Analysis Populations

Population	Description
Per Protocol Set (PPS) (applicable for Part B only)	All randomized participants without any major protocol deviations[a] that could impact the interpretation of efficacy. The PPS will be used for supplemental analyses of the primary and secondary efficacy endpoints.
Safety Set (SS)	All participants who receive at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they actually received. The SS will be used for the analysis of safety data.
OLE Set	All randomized participants who received at least 1 dose of ravulizumab starting from Week 26 (Part A and Part B) onward.
Immunogenicity Analysis Set (IAS)	All participants who receive at least 1 dose of study intervention and have at least one reportable result in the ADA assay. Participants will be analyzed according to the study intervention they actually received

[a] Determination of applicable major protocol deviations for this purpose will be made prior to database lock and study unblinding.
Abbreviations: ADA = antidrug antibody; C5 = complement component 5; OLE = Open-Label Extension; PD = pharmacodynamics; PK = pharmacokinetics

9.4. Statistical Analyses

Statistical methods described in this section will be further detailed in separate SAPs for Part A and Part B for both RCP and OLE Periods. The SAPs will be developed and finalized prior to the database lock of the Randomized Controlled Period for each part. Statistical analyses will include tabulations of summary data, inferential analyses, by-participant listings, and figures. The summary statistics for continuous variables will include, but not be limited to, the number of participants, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented.

All efficacy analyses will be based on the randomized set. Supplemental per-protocol analyses for primary and key secondary efficacy endpoints will be performed based on the Per Protocol Set (PPS) in the same manner as for the randomized set. Safety analyses will be performed on the Safety Set (SS).
The baseline value for analysis and reporting will be based on the last non-missing measurement on or prior to the first dose of study intervention unless stated otherwise.

All data collected during the first 26-week Randomized Controlled Period in Part A will be analyzed independently of Part B and not be included in Part B's formal hypothesis testing.

Analyses will be performed using the SAS® software Version 9.4 or higher.

9.4.1. Efficacy Analyses

This section describes the planned analyses for the primary and key secondary endpoints during the Randomized Controlled Periods for Part A and B. Further details will be provided in the separate SAPs for each part.

9.4.1.1. Efficacy Analysis of Part A

The statistical testing in Part A will be performed with a 2-sided Type 1 error of 0.2 unless stated otherwise.

The estimated treatment effect, 2-sided p-value, and the 2-sided 80% confidence interval (CI) of the treatment effect will be presented.

9.4.1.1.1. Analyses of Primary Efficacy Endpoint for Part A

The primary efficacy analysis will be based on the Randomized Set.

The primary endpoint is TIS≥40 response at Week 26. For the binary composite estimand described in Section 3.1.1, participants experiencing an intercurrent event will be considered non-responders at Week 26, regardless of available TIS data. For all other participants without an intercurrent event, TIS values at Week 26 will be dichotomized into a binary endpoint.

The differences in proportions, along with 2-sided 80% confidence intervals (CIs) using Chan and Zhang method (Chan, 1999), will be presented between the ravulizumab group and the placebo group. Barnard's unconditional exact method will be applied to test whether there is a difference in the proportions of responders between the 2 treatment groups.

Further details, including but not limited to additional sensitivity analyses will be provided in the SAP for Part A.

9.4.1.1.2. Analyses of Secondary Efficacy Endpoints for Part A

A mixed effect repeated measures model will be used to analyze continuous efficacy endpoints. The analysis as stated for the primary endpoint will be used to analyze binary efficacy endpoints and the Cox proportional hazard model will be used for the survival (time-to-event) efficacy endpoints.

Further details will be provided in the SAP for Part A.

9.4.1.2. Efficacy Analysis of Part B

All data collected during the 50-week Randomized Controlled Period in Part B will be analyzed independently of Part A.

The formal statistical hypothesis testing in Part B will be performed with 2-sided Type 1 error of 0.05.

9.4.1.2.1. Analyses of Primary Efficacy Estimand and/or Endpoint for Part B

The primary efficacy analysis will be based on the Randomized Set.

The primary endpoint is defined as TIS≥40 response at Week 50. For the binary composite estimand described in Section 3.1.1, participants will be considered non-responders after experiencing the intercurrent event, regardless of available TIS data. Missing TIS values from participants without intercurrent events will be handled via multiple imputation (MI) assuming missing at random (MAR).

Cochran-Mantel-Haenszel weighting will be used in the estimation of the difference in proportions between treatment and placebo and its variance where the weights account for the

randomization strata (CDASI Activity Score [≤ 14, >14]). If MI is used, Rubin's rule will be used to combine estimates of the difference in proportions and the standard error across the imputations and used to compute the p-value and 95% confidence interval. A 2-sided Type I error of 0.05 and the computed p-value will be used to determine whether the study is considered positive.

The study will be considered positive if the estimated treatment effect favors ravulizumab and the 2-sided p-value is < 0.05.

Further details, including but not limited to the additional sensitivity analyses and subgroup analyses, will be provided in the SAP for Part B.

The planned interim analysis for the sample size re-estimation may also be conducted as described in Section 9.5.

9.4.1.2.2. Sensitivity Analyses for the Primary Estimand for Part B

The following sensitivity analyses will be performed for the primary efficacy endpoint to explore the robustness of the primary efficacy analysis. Additional details will be provided in the SAP for Part B.

Control-Based Multiple Imputation

This sensitivity analysis will assess the robustness of the primary endpoint results due to possible violation of the MAR assumption. Missing TIS40 data will be handled in the same fashion as described in Section 9.4.1.2.1 except that missing TIS data for patients in the ravulizumab group who do not experience intercurrent events will be multiply imputed assuming a trajectory similar to the placebo group.

The same analysis method as described in Section 9.4.1.2.1 will be used.

Tipping Point Analysis:

In this analysis, TIS40 data will be handled in the same fashion as described in Section 9.4.1.2.1 except that missing data from participants in the ravulizumab group who do not experience the intercurrent events will be multiply imputed with an adjustment to the imputed values. The size of the adjustment can be varied and the adjustment which results in a non-significant p-value will be considered the “tipping point”.

9.4.1.2.3. Supplemental Analysis of Primary Endpoint Using Treatment-Policy Estimand

Under the treatment-policy estimand, all available TIS40 data will be used for analysis regardless of whether patients experience intercurrent events. For example, suppose a participant becomes a TIS40 responder after initiation of acute therapy with standard DM treatment. In that case, the observed response will be used, unlike treating the participant as a non-responder described in the primary estimand. Other conventions described in Section 9.4.1.2.1 will remain the same.

9.4.1.2.4. Analyses of Key Secondary Efficacy Endpoint(s) for Part B

The comparison of the treatment groups for the mean IMACS-TIS at Week 50 of the Randomized Controlled Period will be based on the randomized set.

Consistent with the primary composite estimand strategy, for participants who experience the intercurrent events, TIS scores will be assumed to be zero (no improvement) from the point of intercurrent event occurrence. Missing data for other participants will be considered missing at random.

A mixed model for repeated measures will be used for the statistical analysis of the TIS data. The MMRM model will include the observed TIS values at post-baseline visits as the dependent variable. The model will include categorical effects of treatment, study visit, treatment-by-study visit interaction, and the randomization strata. An unstructured covariance matrix will be used to model the correlations among repeated measurements within each participant. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. The least square means, the associated SEs, the p-value and 95% CIs of the mean IMACS-TIS at week 50 for each treatment and difference between ravulizumab and placebo will be calculated.

A control-based imputation and tipping point analysis will also be performed on the mean IMACS-TIS as sensitivity analysis.

A supplemental analysis will also be performed using the Treatment Policy Estimand strategy.

All other continuous key secondary endpoints will be analyzed similarly. Further details will be provided in the SAP for Part B.

9.4.1.2.5. Multiplicity Adjustment for Part B

The primary hypothesis for the primary endpoint will be tested at a 2-sided Type 1 error of 0.05 with statistical inference taking into account the planned-sample size re-estimation (details will be provided in the SAP for Part B) to control the overall Type I error for Part B.

Hypothesis testing associated with the key secondary endpoints will proceed only if the null hypothesis associated with the primary endpoint is rejected.

Holm's method will be used for multiplicity adjustment of the key Part B secondary endpoints.

9.4.2. Safety Analyses

The safety and tolerability of ravulizumab will be assessed based on AE incidence, clinical laboratory findings, ECGs, and vital signs findings. Safety analyses will be performed on the SS population.

9.4.2.1. Analysis of Adverse Events

Analysis and reporting for AEs will be based on treatment-emergent adverse events (TEAEs), including treatment-emergent serious adverse events (TESAEs) and TEAE leading to drug discontinuation, defined as an AE with onset on or after the first dose of study intervention in the Randomized Controlled Period. AEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term, by severity, and relationship to the study intervention. Participant-years adjusted event rates will be generated to characterize the long-term safety profile.

9.4.2.2. Analysis of Clinical Laboratory Parameters, Vital Sign Measurements, and ECG Parameters

Laboratory measurements as well as their changes from baseline at each visit and shift from baseline, if applicable, will be summarized descriptively. Significant findings related to ECG and vital signs will also be summarized using descriptive analyses.

9.4.3. Other Analyses

The following sections describe the general analysis approach to the other endpoints. Further details will be provided in the SAPs for Part A and Part B, respectively.

9.4.3.1. Pharmacokinetic/Pharmacodynamic Analysis

Individual serum concentration data for all participants in the PKAS will be used to derive PK parameters for ravulizumab.

Graphs of mean serum concentration-time profiles will be constructed. Graphs of serum concentration-time profiles for individual participants may also be provided.

Descriptive statistics will be calculated for serum concentration data at each sampling time, as appropriate. Assessment of population-PK may be considered using data from this study or in combination with data from other studies.

Descriptive statistics will be presented for all PD endpoints at each sampling time (see Section 1.3). The PD effects of ravulizumab administered IV will be evaluated by assessing the absolute values and changes and percent changes from baseline in free and total C5 serum concentrations over time, as appropriate. Boxplots of absolute values of free and total C5 serum concentrations by study visit will be constructed. Assessments of ravulizumab PK/PD relationships may be explored using data from this study or in combination with data from other studies.

9.4.3.2. Analysis of Immunogenicity

Analysis of immunogenicity will be based on the IAS.

The presence of ADAs to ravulizumab in serum will be assessed throughout the duration of the study. Further characterization of antibody responses may be conducted as appropriate, including neutralizing antibodies and the titer of confirmed positive samples. Immunogenicity results will be analyzed by summarizing the number and percentage of participants according to their ADA response status. The association of ADAs with ravulizumab concentration, PD parameters, efficacy, and TEAEs may be explored as appropriate.

9.4.3.3. Analysis of Biomarkers

Analyses of exploratory biomarkers will be described in a separate analysis plan.

9.4.3.4. Analyses of Exploratory Endpoint(s)

Analyses of exploratory endpoints will be discussed in the SAP.

9.5. Interim Analyses

9.5.1. Part A Interim Analysis

An unblinded interim analysis may be conducted for futility when approximately 24 (67%) participants complete the Week 26 visit or have discontinued prematurely. The comparative primary and safety data would be assessed in this interim analysis. There is no plan to alter the Part A study design; therefore, no Type 1 error adjustment is needed for the final statistical analysis.

The interim analysis would be conducted by an IDMC to maintain study integrity and blinding. Details of futility criterion, statistical analysis methods, maintenance of study blinding, decision-making and communication plan would be provided in the DMC Charter and the Interim Analysis Plan for Part A.

If the futility criterion is met the Sponsor may stop further enrollment following the IDMC recommendation.
Part B will not be initiated if Part A results in futility or is terminated due to safety concerns.
At the time of the interim analysis there may be additional Part A analyses which may be generated and reviewed by an unblinded team (independent of the study team).

9.5.2. Part B Interim Analysis

An unblinded interim analysis may be conducted for sample size re-estimation using all available TIS data when approximately 30 % of the participants have completed the Week 50 visit or have discontinued prematurely in Part B. The sample size may increase to a maximum of 150 participants in Part B based on the conditional power (Mehta, 2011). Complete details will be included in the SAP. The maximum sample size may be updated once the primary analysis of Part A is completed.

The interim analysis would be performed by an IDMC to maintain study integrity and blinding. Further details of the interim analysis would be provided in the DMC Charter and the Interim Analysis Plan for Part B.

9.6. Data Monitoring Committee

An IDMC, comprising experts in relevant fields with no direct relationship to the study, will be appointed by Alexion. The IDMC will be used for:

- Conduct of interim analyses in Part A and Part B and providing recommendations to the Sponsor (Section 4.1.1, Section 4.1.2, and Section 9.5).
- Monitoring of safety data.

The specific responsibilities of the IDMC and a schedule of meetings will be described in the DMC Charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Management of Potential Infusion-Associated Adverse Events During Study Intervention Administration

IV and infusion-associated reactions are a potential risk with the use of mAbs; these reactions can be nonimmune or immune-mediated (eg, hypersensitivity reactions). Signs and symptoms may include headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, lightheadedness, hypotension, palpitations, and somnolence. Signs and symptoms of hypersensitivity or allergic reactions may include hives, swollen face, eyelids, lips, or tongue, or trouble with breathing.

All administration-, IV-, and infusion-associated reactions will be reported to the Investigator and qualified designee. The Investigator and qualified designee are responsible for detecting, documenting, and recording events that meet the definition of AE or SAE and remain responsible for following up events that are serious, considered related to the study intervention, or study procedures; or that caused the participant to discontinue the study intervention (Section 7).

Definitions and procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.4.

Participants who experience a reaction during the administration of study intervention should be treated according to institutional guidelines.

Participants who experience a severe reaction during administration of study intervention resulting in discontinuation of study intervention should undergo all scheduled safety, PK, and PD evaluations required by the protocol. Alexion must be notified within 24 hours of any infusion reaction requiring interruption or discontinuation of study intervention. All AEs that may indicate an infusion-related response will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) V5.0 or higher.

If anaphylaxis occurs according to the criteria listed in Table 15, then administration of subcutaneous (SC) epinephrine (1/1000, 0.3 mL to 0.5 mL, or equivalent) should be considered. In the case of bronchospasm, treatment with an inhaled beta agonist also should be considered. Participants administered an antihistamine for the treatment or prevention of an infusion reaction should be given appropriate warnings about drowsiness and impairment of driving ability before being discharged from the center.

Table 18: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:
• Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least 1 of the following: o Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

Table 18: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:
○ Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
• Two or more of the following that occur rapidly after exposure to a likely allergen for that participant (minutes to several hours): ○ Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips/tongue/uvula) ○ Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia) ○ Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) ○ Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
• Reduced BP after exposure to known allergen for that participant (minutes to several hours): ○ Systolic BP of less than 90 mmHg or greater than 30% decrease from that participant's baseline

Abbreviations: BP = blood pressure; PEF = peak expiratory flow
Source: (Sampson, 2006)

10.2. Regulatory, Ethical, and Study Oversight Considerations

10.2.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and 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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations

  The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator/Alexion and reviewed and approved by the IRB/IEC before the study is initiated.
  - If any of these documents require regulatory/health authority approval per local regulations, Alexion will also obtain such approval before the study is initiated.
- Any substantial amendments to the protocol will require IRB/IEC and regulatory/health authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC EU CTR 536/2014 for clinical studies and all other applicable local regulations
  - Promptly notifying Alexion of any (potential) serious breach of the protocol or regulations (including if a data breach compromises the integrity, confidentiality, or availability of the personal data of participants) so that legal and ethical obligations are met. A ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- In certain regions/countries, Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about serious breaches. Alexion will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority (including data protection authorities and, if

applicable, affected participants in case of a personal data breach), IRB/IEC, and Investigators.

- The Investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach, including personal data breaches
  - A (potential) serious breach is promptly reported to Alexion or delegated party, through the contacts (email address or telephone number) provided by Alexion.
- The Sponsor and the site have taken all necessary steps to avoid personal data breaches and have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining, and keeping systems and information technology security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- Both the Sponsor and the site have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- In compliance with applicable laws, the data controller for the processing activity where the personal data breach occurred (the Sponsor or respectively the site) will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- If the personal data breach needs to be notified to participants, the notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the data controller and for data breaches occurred within the processing activities of the Sponsor as the data controller, the notification is done in collaboration with the site and is performed by the site and/or Investigator, acting on behalf of the Sponsor, so that the Sponsor has no access to the identifying personal information of the participants. The site and/or Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by the Sponsor, the processor under contractual obligations with the Sponsor promptly and in due course after discovering the breach notifies the Sponsor and provides full cooperation with the investigation. In these cases, to the extent the Sponsor is the data controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or Investigator, acting on behalf of the Sponsor, so that the Sponsor has no access to the identifying personal information of the participants.
- Where a personal data breach is suffered by the Study Monitor, the latter will provide the Sponsor with all of the information needed for notification of the breach, without

disclosing data that allows the Sponsor directly or indirectly to identify the participants. The notification will be done by the Sponsor solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of reidentification of the participants. If the data breach must be notified to the data participants, the notification will be done directly by the Study Monitor in collaboration with the site and/or Investigator, acting on behalf of the Sponsor, so that the Sponsor has no access to the identifying personal information of the participants. The contract between the Sponsor and the Study Monitor shall expressly specify these conditions.

- The contract between the site and the Sponsor for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

10.2.2. Financial Disclosure

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

10.2.3. Informed Consent Process

- It is the responsibility of the Investigator or designee to obtain signed (written or electronic signature) informed consent from all study participants, or the participant's legally authorized representative, prior to performing any study-related procedures including screening assessments.
- The Investigator or designee will explain the nature of the study (including but not limited to the objectives, potential benefits and risks, inconveniences, and the participant's rights and responsibilities) to the participant or his/her legally authorized representative, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent or a certified translation, if applicable, that meets the requirements of 21 CFR 50, local regulations, EU General Data Protection Regulation (GDPR), ICH GCP guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The participant's medical record must include a statement that signed (written or electronic) informed consent was obtained before any screening procedures were performed with a participant, and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study, as applicable.

- A copy of the signed (written or electronic) informed consent documentation (ie, a complete set of participant information sheets and fully executed signature pages) must be provided to the participant or the participant's legally authorized representative, as applicable. This document may require translation into the local language. Original signed (written or electronic) consent forms must remain in each participant's study file and must be available for verification at any time.

Participants who are rescreened outside of the Screening window (Section 1.3) are required to sign a new ICF (Section 5.4).

10.2.4. Recruitment Strategy

Participants will be identified by qualified research staff. This may be done through a review of medical records, external referrals or using databases. Recruitment strategies may include study posters, referral letters, recruitment brochures, advertisements, social media posts, and websites, where permitted by local regulations. All recruitment materials will be submitted to local IRB/EC as required, for review and approval for use.

10.2.5. Data Protection

- Participants will be assigned a unique identifier by a Trusted Third Party contracted by Alexion or by a Principal Investigator. Any participant records or datasets that are transferred to Alexion will contain the identifier only; participant names, initials, or any information which would make the participant identifiable will not be transferred.
- Participants must be informed that their personal study-related and coded (pseudonymized) data will be used in accordance with applicable data protection law, and participants must also be informed of any individuals rights they may have with regard to their personal data. Participants will be informed about how their personal study-related data will be disclosed, and will be required to agree to the information contained in the informed consent and provide consent to the processing of their personal data, if required by applicable data protection law.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, appropriate IRB/IEC members, and inspectors from regulatory authorities.
- Alexion as a data controller has implemented privacy and security controls designed to help protect participant personal data; including information security controls, firewalls, incident detection, and secure transfer measures.
- The contract between Alexion and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful, loss, alteration, or unauthorized disclosure or access.

- The General Data Protection Regulation defines pseudonymization as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.
- Appropriate safeguards will be implemented to protect coded data during and after the study that include:
  - Access to the coded data will be limited to specific individuals subject to confidentiality obligations (including the obligation to not attempt to re-identify individuals/decode the clinical data).
  - The coded data will be protected with security measures to avoid data alteration, loss, and unauthorized accesses and further de-identification techniques may be applied.
  - A data protection impact assessment, where required, will apply to identify and mitigate privacy risks, if any, associated with each scientific research.
  - The coded data will not be shared for direct marketing purposes or other purposes that are not legal duties or are not considered scientific research according to the applicable data protection legislation. In particular, it will not be used to make decisions about future services available to the participant, such as insurance.
- In addition to having the participants' data and biosamples coded, the data are also protected by high-standard technical security means, such as strong access control and encryption.
- Participants are also protected legally by the following means if the level of disclosure of the coded data includes sharing of the latter with other third parties, as the participants will be explained in the ICF:
  - The participants' coded data are protected by contractual arrangements, Codes of Conduct, or certifications that set the rules for personal information protection to those available in European countries or other alternatives set forth in the law, as well as any supplementary technical and organizational measures that may results out of conducted transfer impact assessments.

10.2.6. Dissemination of Clinical Study Data

Study-related information and study results 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. However, posting of study results per local regulations may be deferred to a later date for one of the following reasons:

- Study is still ongoing in other countries or regions

- Study is part of an ongoing review for approval by Health Authorities; study result data deferral request can be submitted.

10.2.7. Data Quality Assurance

- All participant data relating to the study will be recorded on paper or eCRFs unless transmitted to Alexion or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Alexion or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
  - Remote source data verification may be employed where permitted by local regulations.
  - The scope of the source data verification will be described in detail in the Clinical Monitoring Plan.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 30 years after study completion or longer as per local regulations or institutional policies. No records may be destroyed without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion. Clinical study documents and records required as part of the TMF are archived and stored by Alexion for at least 30 years.
- Quality tolerance limits (QTLs) will be predefined in the study-specific risk register to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

10.2.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The Investigator or designee will prepare and maintain adequate and accurate source documents (eg, medical records, ECGs, AE and concomitant medication

reporting, raw data collection forms) designed to record all observations and other pertinent data for each participant.

Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. eCRFs must be completed by the Investigator or designee as indicated in the site delegation log. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available to Alexion, Alexion delegates, and health authorities, as requested. Source documents are filed at the investigational site.

Per ICH E6 (R2) guidelines and good documentation practice requirements, source documents and study records in all media (eg, paper, electronic) must be Attributable, Legible, Contemporaneous, Original, Accurate, and Complete.

10.2.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants (ie, first site activation).

Alexion reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion. Study sites will be closed after the study is completed or following the decision to close or terminate the study. A study site is considered closed when all participants have completed the EOS or ET Visit, all data have been collected and entered into the electronic data capture (EDC) system, all required documents and study supplies have been collected and reconciled, and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by Alexion or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Alexion's procedures, or ICH GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discovery of an unexpected, serious, or unacceptable risk of the study drug to participants enrolled or continuing in the study
- Discontinuation of further study intervention development

If futility criteria are met or if the benefit/risk is not considered favorable, the Sponsor may stop further enrollment in the study, under guidance from an IDMC.

Part B will not be initiated if Part A results in futility or is terminated due to safety concerns. If the study is prematurely terminated or suspended, Alexion shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.2.10. Publication Policy

- Where possible, primary manuscripts reporting results of the primary efficacy endpoint or the final results will be submitted for publication within 12 to 18 months of the primary evaluation date or end of study, whichever is earlier.
- Investigators who participate as authors in manuscripts derived from Alexion sponsored studies will agree to the prerequisites as outlined in the Alexion author engagement agreement prior to engaging in manuscript development.
- The Investigator agrees to submit proposals for new manuscripts (whether or not the proposed analyses are derived from protocol specified endpoints) to Alexion for review and consideration. All manuscripts or abstracts emanating from approved proposals are to be submitted to Alexion for review before submission to the journal/society. This allows Alexion to protect proprietary information and provide comments.
  - The proprietary nature of some development work may preclude publication. In some cases, it may be necessary to delay a publication to allow Alexion to ensure protection of intellectual property.
- Primary publications, including congress and journal publications, containing the protocol-specified results of a study should occur prior to the publication of individual study site results or case reports. Alexion's policy prohibits duplicate publication, whereby the same results must not be published in multiple peer-reviewed journal manuscripts.
  - Encore congress publications may be appropriate to allow communication of research findings to relevant audience and geographical regions.
- Alexion will comply with the requirements for publication of study results as defined by the Pharmaceutical Research and Manufacturers of America and the International Committee of Medical Journal Editors and per the Alexion Publication Policy. In accordance with standard editorial and ethical practice, Alexion will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements and per the Alexion Publication Policy.
- Alexion will Publish Patient Lay Summaries and include participants and/or caregivers as reviewers for readability and understanding of lay person language.

10.2.11. Good Clinical Practice Compliance

Alexion and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 R2, EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of Alexion and/or the company organizing/managing the research on behalf of Alexion to inspect study data, participants' medical records, and eCRFs in accordance with current GCP and respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

Alexion ensures that local regulatory authority requirements are met before the start of the study. Alexion (or designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of ravulizumab for shipment to the site.

10.3. Clinical Laboratory Tests

- The tests detailed in Table 19 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be available in the participant's source documents.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing: women of childbearing potential should only be enrolled after a negative serum or urine pregnancy test. Urine pregnancy testing will be standard for the protocol unless serum testing is required by local regulation or ethics committees and should be performed at the time points specified in the SoA (Section 1.3).

Table 19: Laboratory Assessments

Laboratory Assessments	**Parameters**		
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC indices: Distribution width Mean corpuscular volume Mean corpuscular Hemoglobin %Reticulocytes	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	BUN C-reactive protein Creatinine Chloride Potassium Bicarbonate Sodium Glucose (non-fasting) Calcium Magnesium	Creatine kinase Aldolase LDH AST ALT Alkaline phosphatase Gamma glutamyltransferase	Total and direct bilirubin Total protein Albumin Uric acid
Coagulation	International normalized ratio, partial thromboplastin time, prothrombin time		

Table 19: Laboratory Assessments

Laboratory Assessments	Parameters
Urinalysis	Appearance, color, specific gravity, pH, glucose, protein, leukocyte esterase, blood, ketones, bilirubin, urobilinogen, nitrite, microscopic examination (if blood or protein is abnormal)
Other screening tests	Serum/urine β-HCG pregnancy test (as needed for participants of childbearing potential)[a] Serum follicle-stimulating hormone test to be performed at Screening in selected female participants to confirm postmenopausal status HIV-1 and HIV-2 antibodies
Complement activity	Free C5 Total C5
Other	Antidrug antibodies

[a] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committees.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C5 = complement component 5; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; RBC = red blood cells; WBC = white blood cells

10.4. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A). • **Note**: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease [new or exacerbated] temporally associated with the use of the study intervention, whether or not considered related to the study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events Not Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): The condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the signing the ICF, admissions for social reasons or for convenience). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error. • Cases of pregnancy that occur during maternal or paternal exposure to study intervention are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation.

Events Not Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

10.4.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it was more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
4. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-

An SAE is defined as any untoward medical occurrence that, at any dose:

threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

A suspected unexpected serious adverse reaction (SUSAR) is defined as:

An event that is assessed as serious by the Investigator and/or Alexion that is not listed in the appropriate Reference Safety Information (IB) and has been assessed that there is at least a reasonable possibility that the event is related to the investigational medicinal product by the Investigator and/or Alexion.

Alexion has procedures that will be followed for the recording, medical assessment, and expedited reporting of SUSARs that are consistent with global regulations, legislation, and guidance documents.

Suspected unexpected serious adverse reactions will undergo expedited reporting to the national regulatory authorities, IRBs/IECs, and Investigators following local regulatory reporting requirements where applicable.

10.4.3. Recording and Follow-Up of AE and/or SAE

Recording of AE and/or SAE

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to Alexion in lieu of completion of the Alexion AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Alexion. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Alexion.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories from National Cancer Institute CTCAE v5.0, published 27 Nov 2017:

- Grade 1: Mild (awareness of sign or symptom, but easily tolerated)
- Grade 2: Moderate (discomfort sufficient to cause interference with normal activities)
- Grade 3: Severe (incapacitating, with inability to perform normal activities)
- Grade 4: Life-threatening
- Grade 5: Fatal

Recording of AE and/or SAE

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study intervention and each occurrence of each AE or SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the eCRF and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - Not related: There is no reasonable possibility the study intervention caused the AE.
    (a) The AE has a more likely alternative etiology; it may be due to underlying or concurrent illness, complications, concurrent treatments, or effects of another concurrent drug.
    (b) The event does not follow a reasonable temporal relationship to administration of the study intervention.
  - Related: There is a reasonable possibility the study intervention caused the AE.
    (c) The AE has a temporal relationship to the administration of the study intervention.
    (d) The event does not have a likely alternative etiology.
    (e) The event corresponds with the known pharmaceutical profile of the study intervention.
    (f) There is improvement on discontinuation and/or reappearance on rechallenge.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Alexion. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Alexion.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Alexion to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Follow-up of AEs and SAEs
• If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Alexion with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The Investigator will submit any updated SAE data to Alexion within 24 hours of receipt of the information.

10.4.4. Reporting of SAEs

SAE Reporting to Alexion via an Electronic Data Collection Tool
• All SAEs will be recorded and reported to Alexion immediately and within 24 hours of awareness. • The primary mechanism for reporting an SAE to Alexion will be the EDC system. • If the electronic system is unavailable or site staff is unable to process the SAE via the EDC system at the time that the Investigator or site becomes aware of an SAE, the site will use the paper Contingency Form for SAE Reporting via facsimile or email. Facsimile transmission or email may also be used in the event of electronic submission failure. – Email: clinicalsae@alexion.com or Fax: + 1.203.439.9347 • The site will enter the SAE data into the EDC system as soon as it becomes available. • When further information becomes available, the EDC should be updated immediately with the new information and an updated SAE report should be submitted to Alexion Global Patient Safety (GPS) within 24 hours of Investigator/site awareness. • After the participant has completed the study, no new data or changes to existing data are expected to be entered in the EDC system. o If a site receives a report of a new SAE from a study participant which the Investigator considers to be related to the study intervention, or the site receives updated data on a previously reported SAE after the EDC system has been taken offline, then the site can report this information on a paper Contingency Form for SAE Reporting via facsimile or email.

10.4.5. Unexpected Events

Apart from the reporting of SUSARs, there may be other events which are relevant in terms of benefit-risk balance and which should be reported in a timely manner according to regional and national requirements. It is important for participant safety that, in addition to SAEs and reactions, all unexpected events that might materially influence the benefit-risk assessment of the study intervention or that would lead to changes in the administration of the study intervention or in overall conduct of a clinical study should be reported. Examples of such unexpected events include an increase in the rate of occurrence of expected serious adverse reactions which may be clinically important, a significant hazard to the patient population, such as lack of efficacy of a medicinal product, or a major safety finding from a newly completed animal study (such as, carcinogenicity).

Under the EU CTR 536/2014 (49), where unexpected events require an urgent modification of a clinical study, Alexion and the Investigator may need to take urgent safety measures without awaiting prior authorization. If such measures constitute a temporary halt of the clinical study, Alexion will apply for a substantial modification before restarting the clinical study.

10.5. Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

Any events of medication error, with or without associated AEs, are to be captured and forwarded to Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Medication Error Report Form.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, eg, wrong route, wrong device, or wrong site of administration
- Drug not stored as instructed, eg, kept at room temperature when it should be stored in the refrigerator
- Wrong participant received the medication (excluding IRT errors)
- Wrong drug administered to participant (excluding IRT errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT - including those which led to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this clinical study, drug abuse is defined as the persistent or sporadic intentional, nontherapeutic excessive use of study intervention for a perceived reward or desired nontherapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Drug Misuse or Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of study intervention for medicinal purposes outside of the authorized product information, or for unauthorized study intervention, outside the intended use as specified in the protocol, including deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Drug Misuse or Drug Abuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault on another person
- The drug is deliberately administered by the wrong route
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

10.6. Contraceptive Guidance and Collection of Pregnancy Information

10.6.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the Following Categories Are Not Considered WOCBP

1. Premenarchal
2. Premenopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral tubal ligation or bilateral salpingectomy
    - Documented bilateral oophorectomy

    For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

    Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause prior to the Day 1 Visit.
        - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement may be required. In the absence of 12 months of amenorrhea the reason for not obtaining FSH levels should be documented by the Investigator at the time of Screening.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
4. Permanent sterilization at least 6 weeks prior to the Day 1 Visit.

10.6.2. Contraception Guidance

Contraceptive use by male or female participants should be consistent with local regulations regarding the methods of contraception utilized for those participating in clinical studies. If

teratogenic effects are suspected to be transferred to a fetus/embryo from a female spouse/partner of a male participant, pregnancy follow-up information will be obtained for the partner who becomes pregnant (refer to Section 10.5.3.1). In these cases, follow-up will be conducted on the pregnant partner in the same manner as a female participant who becomes pregnant during the study.

10.6.2.1. Guidance for Female Participants

Female participants of childbearing potential must use a highly effective or acceptable method of contraception, including at least 1 of the following until at least 8 months after the final dose of study intervention.

1. Intrauterine device in place for at least 6 weeks prior to first dose of study intervention.
2. Progestogen-only hormonal contraception associated with inhibition of ovulation (either oral, injectable, or implantable) for at least 6 weeks prior to first dose of study intervention.
3. Intrauterine progestogen releasing system for at least 6 weeks prior to first dose of study intervention.
4. Bilateral tubal occlusion for at least 6 weeks prior to first dose of study intervention.
5. Combined (estrogen- and progestogen-containing) hormonal contraception (either oral, intravaginal, or transdermal) for at least 6 weeks prior to first dose of study intervention.
6. Surgical sterilization of the male partner (medical assessment of azoospermia is required if vasectomy was performed within 6 months prior to first dose of study intervention). Male partner is still required to use condom during sexual intercourse.
7. Sexual abstinence for female participants:
    a. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the participant's preferred and usual lifestyle. Abstinent female participants must refrain from heterosexual intercourse for at least 8 months after the final dose of study intervention.

Other methods of contraception that are not considered as highly effective for female participants, but are acceptable birth control methods (that result in a failure rate of more than 1% per year) include:

8. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action;
9. Male or female condom with or without spermicide
10. Cap, diaphragm, or sponge with spermicide
11. A combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier methods)

Female participants must not donate ova from the Day 1 Visit at least until 8 months after their final dose of study intervention.

The following methods of contraception are considered unacceptable in this study:

- Periodic abstinence (calendar, symptothermal, or post-ovulation methods
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method
- Female condom and male condom should not be used together

10.6.2.2. Guidance for Male Participants

Contraception is the responsibility of the heterosexually active male participants in the study, regardless of his female partner's method of contraception.

Male participants who have had a vasectomy > 6 months prior to the first dose of study intervention must use a condom during heterosexual intercourse. Male participants who have had a vasectomy < 6 months prior to the first dose study intervention and those who have not had a vasectomy must use a condom and spermicide during heterosexual intercourse for at least 8 months after their final dose of study intervention.

Participants with a spouse/partner of childbearing potential or a pregnant or breastfeeding spouse or partner must agree to use double barrier contraception (male condom plus appropriate barrier method for the female partner) while on treatment and for at least 8 months after the last dose of study intervention. Double barrier contraception is required even with documented medical assessment of surgical success of a vasectomy.

Male participants must not donate sperm from the Day 1 Visit until 8 months after their final dose of study intervention.

10.6.2.2.1. Sexual Abstinence for Male Participants

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the participant's preferred and usual lifestyle. Abstinent male participants who become heterosexually active must use a condom and spermicide during intercourse.

Periodic abstinence (eg, calendar, symptothermal, or post-ovulation methods for a female partner) is not considered a highly effective method of contraception for male participants.

10.6.3. Collection of Pregnancy Information

Pregnancy data will be collected during this study for all female participants and female spouses/partners of male participants from the first dose of study intervention until the EOS Visit.

Any female participant who becomes pregnant during the study should be discontinued from the study intervention.

Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of study intervention via semen following paternal exposure. If a female participant or a male participant's female spouse/partner becomes pregnant during the

conduct of this study, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome Form" to Alexion GPS via facsimile or email. When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GPS. If additional follow-up is required, the Investigator will be requested to provide the information.

Exposure of an infant to study intervention during breastfeeding must also be reported (via the "Pregnancy/Breastfeeding Reporting and Outcome Form") and any AEs experienced by the infant must be reported to Alexion GPS via email or facsimile.

Pregnancy is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs.

10.6.3.1. Male Participants with Partners Who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate "Pregnancy/Breastfeeding Reporting and Outcome Form" and submit it to Alexion within 24 hours of learning of the partner's pregnancy. 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 Alexion. Generally, the follow-up will be no longer than 3 months following the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.6.3.2. Female Participants Who Become Pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The information will be recorded on the "Pregnancy/Breastfeeding Reporting and Outcome Form" and submitted to Alexion within 24 hours of learning of a participant's pregnancy.
- For all Alexion products, both in development or post-approval, exposure during pregnancy must be recorded and the pregnancy followed, until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the participant discontinues the study intervention or withdraws from the study. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to Alexion. Generally, follow-up will not be required for longer than 3 months beyond the estimated delivery date. 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 AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be

reported as an AE or SAE. A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) 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 intervention by the Investigator will be reported to Alexion. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

10.7. Biomarkers

- Blood will be collected in all the study sites. All biomarker analyses and the data will be used for research (eg, exploratory) related to ravulizumab or DM and related diseases. The samples may also be used to develop tests/assays including diagnostic tests related to ravulizumab and/or other C5 inhibitors and DM.
- The samples may be analyzed as part of a multistudy assessment of biomarkers in the response to ravulizumab or C5 inhibitors to understand study disease or related disease.
- The results of biomarker analyses may be reported in the Clinical Study Report or in a separate study summary.
- Alexion or designee will store the samples obtained for biomarker analyses in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on ravulizumab or C5 inhibitors continues but no longer than 5 years after all data have been collected for the study or other period/time point per local requirements.

10.8. Clinical Outcome Assessments

10.8.1. Myositis Disease Activity Assessment Tool (MDAAT)

IMACS FORM 07A: MYOSITIS DISEASE ACTIVITY ASSESSMENT TOOL (MDAAT) – 2005, VERSION 2

General Guidelines for Completion:
This is a combined tool that captures the physician's assessment of disease **activity** of various organ systems using (1) the 0-4 scale described below and (2) a visual analog scale (VAS). Please assess the clinical features (items 1-26) of each organ system based upon:

a) The presence of clinical features or symptoms **within the previous 4 weeks that are due to active disease** (i.e. use your clinical judgment to determine how active the myositis-associated clinical feature has been **within the previous 4 weeks**)
b) The judgment that the feature is due to the myositis disease process (i.e. clinical findings known or suspected to be due to another disease process or due to therapy should **NOT** be considered in this evaluation)
c) The concept that disease activity is defined as a potentially reversible finding
d) A clinical, functional, and laboratory assessment for each organ system:
NA = Cannot be assessed
0 = Not present in the last 4 weeks
1 = Improving - clinically significant improvement in the last 4 weeks compared to the previous 4 weeks
2 = The same - manifestations that have been present for the last 4 weeks without significant improvement or deterioration compared to the previous 4 weeks
3 = Worse - clinically significant deterioration over the last 4 weeks compared to the previous 4 weeks
4 = New - in the last 4 weeks (compared to the previous 4 weeks)

Also, rate your overall (global) assessment of the ongoing disease activity over the past 4 weeks for each organ system on the 0-10cm VAS scale (which precedes the listed clinical features) by drawing a **vertical** mark on the 10cm line according to the following guidelines:

- left end of line = no evidence of disease activity
- midpoint of line = moderate disease activity
- right end of line = extreme or maximum disease activity

Please review the glossary as you score each listed clinical feature. The VAS score for each organ system integrates the severity of activity based upon all of the clinical features listed for that particular organ system.

NOTE: The "Extramuscular Global Assessment" is very important as this is a Core Set Measure encompassing an overall evaluation for the disease activity in all the extramuscular organ systems and excludes muscle disease activity.

Guidelines for scoring mild, moderate, severe:
First, identify the category of mild-severe **using the glossary as a guide**. Then score what has happened in the last 4 weeks compared to the previous 4 weeks. Note that with worsening (3) or new (4) activity in the designated category, the same degree of activity should be ascribed in the items that are "less severe." For example:

- In a patient developing new moderate muscle inflammation (see glossary for definition) in the last 4 weeks, "moderate muscle inflammation" (25b) would score a 4 as would "mild muscle inflammation" (25c)
- If "severe muscle inflammation" worsened in the last 4 weeks, then the severe (25a), moderate (25b) and mild (25c) muscle inflammation categories would all score a 3

If a patient had severe muscle inflammation at last visit one month ago and improves to a moderate category over the past 4 weeks (based on the glossary definition), then score the severe category (25a) as a 1 (improving) and score moderate (25b) and mild (25c) as either a 1 or 2 (this would depend on just how much improvement has occurred over the last month so the glossary should be reviewed for this). If one month later the symptoms have further improved, then score the severe category (25a) as a 0 and the moderate (25b) and mild (25c) categories as a 1.

MDAAT (Continued)

IMACS FORM 07a: MYOSITIS DISEASE ACTIVITY ASSESSMENT TOOL – 2005, Version 2

Subject's IMACS number: _____ **ASSESSOR:** _____ **Date Assessed:** _____ **Assessment number:** ____

Constitutional Disease Activity	(Absent) — (Maximum) ___.__ cm	Examples of maximal score: Severe fatigue or malaise resulting in being bed bound and an inability to perform self care					
1. Pyrexia – documented fever > 38° Celsius		0	1	2	3	4	NA
2. Weight loss – unintentional > 5%		0	1	2	3	4	NA
3. Fatigue/malaise/lethargy		0	1	2	3	4	NA

Cutaneous Disease Activity	(Absent) — (Maximum) ___.__ cm	Examples of maximal score: - Ulceration to muscle, tendon or bone; - Extensive erythroderma					
4. Cutaneous ulceration		0	1	2	3	4	NA
5. Erythroderma		0	1	2	3	4	NA
6. Panniculitis		0	1	2	3	4	NA
7. Erythematous rashes:							
a. **with** secondary changes (e.g. accompanied by erosions, vesiculobullous change or necrosis)		0	1	2	3	4	NA
b. **without** secondary changes		0	1	2	3	4	NA
8. Heliotrope rash		0	1	2	3	4	NA
9. Gottron's papules/sign		0	1	2	3	4	NA
10. Periungual capillary changes		0	1	2	3	4	NA
11. Alopecia:							
a. Diffuse hair loss		0	1	2	3	4	NA
b. Focal, patchy with erythema		0	1	2	3	4	NA
12. Mechanics hands		0	1	2	3	4	NA

MDAAT (Continued)

Skeletal Disease Activity	(Absent) — (Maximum) __ __ . __ cm	Examples of maximal score: Severe arthritis with extreme loss of function (bedridden, inability for self care)

13. Arthritis:						
a. Severe active polyarthritis	0	1	2	3	4	NA
b. Moderately active arthritis	0	1	2	3	4	NA
c. Mild arthritis	0	1	2	3	4	NA
14. Arthralgia	0	1	2	3	4	NA

Gastrointestinal Disease Activity	(Absent) — (Maximum) __ __ . __ cm	Examples of maximal score: Major abdominal crisis requiring surgery or intensive care

15. Dysphagia:						
a. Moderate/severe dysphagia	0	1	2	3	4	NA
b. Mild dysphagia	0	1	2	3	4	NA
16. Abdominal pain related to the myositis disease process:						
a. Severe	0	1	2	3	4	NA
b. Moderate	0	1	2	3	4	NA
c. Mild	0	1	2	3	4	NA

Pulmonary Disease Activity	(Absent) — (Maximum) __ __ . __ cm	Examples of maximal score: Active interstitial lung disease or respiratory muscle weakness requiring ventilatory support

17. Respiratory muscle weakness **without** interstitial lung disease (ILD):						
a. Dyspnea at rest	0	1	2	3	4	NA
b. Dyspnea on exertion	0	1	2	3	4	NA
18. **Active reversible ILD** (i.e. not just ventilatory abnormalities due to pulmonary fibrosis): *Read glossary for scoring pulmonary function tests and score each item below (a,b and c).*						
a. Dyspnea or cough due to ILD	0	1	2	3	4	NA
b. Parenchymal abnormalities on chest x-ray or high resolution CT scan (HRCT) and/or ground glass shadowing on HRCT	0	1	2	3	4	NA
c. Pulmonary Function Tests: ≥ 10% change in FVC OR ≥ 15% change in DLCO	0	1	2	3	4	NA
19. Dysphonia:						
a. Moderate to severe	0	1	2	3	4	NA
b. Mild	0	1	2	3	4	NA

IMACS Form 07a: Myositis Disease Activity Assessment Tool – 2005, Version 2, updated 2015

Page 2 of 3

MDAAT (Continued)

Cardiovascular Disease Activity	(Absent) ——— (Maximum) ___.__ cm	**Examples of maximal score** Myocarditis, pericarditis or severe arrhythmia requiring intensive care unit

20. Pericarditis	0	1	2	3	4	NA
21. Myocarditis	0	1	2	3	4	NA
22. Arrhythmia:						
a. Severe arrhythmia	0	1	2	3	4	NA
b. Other arrhythmia, except sinus tachycardia	0	1	2	3	4	NA
23. Sinus tachycardia	0	1	2	3	4	NA

Other Disease Activity	(Absent) ——— (Maximum) ___.__ cm	**Examples of maximal score** Extreme disease activity with major impact on function

24. Specify:_____	0	1	2	3	4	NA

Extramuscular Global Assessment	(Absent) ——— (Maximum) ___.__ cm	Overall evaluation for disease activity in all extramuscular systems **(EXCLUDING MUSCLE DISEASE ACTIVITY)**

Muscle Disease Activity	(Absent) ——— (Maximum) ___.__ cm	**Examples of maximal score** Severe muscle weakness resulting in being bed bound and an inability to perform self care

25. Myositis:						
a. Severe muscle inflammation	0	1	2	3	4	NA
b. Moderate muscle inflammation	0	1	2	3	4	NA
c. Mild muscle inflammation	0	1	2	3	4	NA
26. Myalgia	0	1	2	3	4	NA

Global Disease Activity	(Absent) ——— (Maximum) ___.__ cm	Overall evaluation for the totality of disease activity in ALL systems, **(INCLUDING MUSCLE DISEASE ACTIVITY)**

IMACS Form 07a: Myositis Disease Activity Assessment Tool – 2005, Version 2, updated 2015

Page 3 of 3

10.8.2. Physician Global Activity Assessment

IMACS FORM 02: PHYSICIAN GLOBAL ACTIVITY ASSESSMENT

Subject's IMACS number _____

Assessor _____

Date of assessment (mm/dd/yy) _____

Assessment number _____

Physician Global Activity Assessment

Disease Activity is defined as potentially reversible pathology or physiology resulting from the myositis. Clinical findings known or suspected to be due to another disease process should not be considered in this evaluation. The global assessment of disease activity is to be judged from all the information available to you today including the subject's appearance, history, physical examination, diagnostic laboratory testing and your resultant medical therapy.

Please rate your global (overall) disease activity assessment by drawing a vertical mark on the 10-cm. line below according to the following scale: left end of line = no evidence of disease activity, midpoint of line = moderate disease activity, and right end of line = extremely active or severe disease activity.

No evidence of disease activity — Extremely active or severe disease activity

Also rate global disease activity on a 5-point Likert scale:

◯ 0 = none
◯ 1 = mild activity
◯ 2 = moderate activity
◯ 3 = severe activity
◯ 4 = extremely severe activity

10.8.3. Patient Global Activity Assessment

IMACS FORM 03: PATIENT/PARENT GLOBAL ACTIVITY ASSESSMENT

Subject's IMACS number _____

Assessor _____ _____

Assessor's relationship to subject: ◯Patient; ◯Mother; ◯Father; ◯Other (specify):_____

Date of assessment (mm/dd/yy) _____

Assessment number _____

Your myositis is the result of the combined effects of many disease processes. One of these is disease activity, which is active inflammation in your/your child's muscles, skin, joints, intestines, heart, lungs or other parts of your body, which can improve when treated with medicines.

1. Considering all the ways that myositis affects you/your child, please rate the overall activity of your/your child's disease today by placing a mark on the line below.

No evidence of disease activity

Extremely active or severe disease activity

IMACS FORM 03:PATIENT/PARENT GLOBAL ACTIVITY ASSESSMENT

10.8.4. Manual Muscle Test (MMT-8)

Manual Muscle Testing Scoring Sheet

Muscle Groups	Right (0 – 10)	Left (0 – 10)	Axial (0 – 10)
Axial Muscles (0 – 10)			
1. Neck Flexors			
Proximal Muscles (0 – 100)			
2. Deltoid middle			
3. Biceps brachii			
4. Gluteus maximus			
5. Gluteus medius			
6. Quadriceps			
Distal Muscles (0 – 40)			
7. Wrist Extensors			
8. Ankle dorsiflexors			
Totals			
MMT8 score (0 – 150)			

MMT8 is a set of 8 designated muscles, 7 measured *bilaterally* + Neck Flexors, for a potential total score 0 – 150.

Axial score: 0 – 10 potential range: sum of neck flexors and extensors

Proximal score: 0 – 100 potential range; 5 muscle groups tested *bilaterally*

Distal score: 0 – 40 potential range; 2 muscle groups tested *bilaterally*

10.8.5. Health Assessment Questionnaire (HAQ)

Header to be completed by study site

Study Number: ALXN1210-DM-310 Subject ID: _____

Date Completed: _____ Time Completed: _____

HEALTH ASSESSMENT QUESTIONNAIRE

Name_____ **Date**_____

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
DRESSING & GROOMING				
Are you able to:				
- Dress yourself, including tying shoelaces and doing buttons?	____	____	____	____
- Shampoo your hair?	____	____	____	____
ARISING				
Are you able to:				
- Stand up from a straight chair?	____	____	____	____
- Get in and out of bed?	____	____	____	____
EATING				
Are you able to:				
- Cut your meat?	____	____	____	____
- Lift a full cup or glass to your mouth?	____	____	____	____
- Open a new milk carton?	____	____	____	____
WALKING				
Are you able to:				
- Walk outdoors on flat ground?	____	____	____	____
- Climb up five steps?	____	____	____	____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

_____ Cane
_____ Walker
_____ Crutches
_____ Wheelchair
_____ Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)
_____ Built up or special utensils
_____ Special or built up chair
_____ Other (Specify:_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

_____ Dressing and Grooming
_____ Arising
_____ Eating
_____ Walking

1 ©S

HAQ-DI – United States/English
HAQ-DI_AU1.0-eng-USorl.doc

Health Assessment Questionnaire (HAQ) - Continued

Header to be completed by study site	
Study Number: ALXN1210-DM-310	Subject ID: _____
Date Completed: _____	Time Completed: _____

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
HYGIENE				
Are you able to:				
- Wash and dry your body?	____	____	____	____
- Take a tub bath?	____	____	____	____
- Get on and off the toilet?	____	____	____	____
REACH				
Are you able to:				
- Reach and get down a 5 pound object (such as a bag of sugar) from just above your head?	____	____	____	____
- Bend down to pick up clothing from the floor?	____	____	____	____
GRIP				
Are you able to:				
- Open car doors?	____	____	____	____
- Open jars which have been previously opened?	____	____	____	____
- Turn faucets on and off?	____	____	____	____
ACTIVITIES				
Are you able to:				
- Run errands and shop?	____	____	____	____
- Get in and out of a car?	____	____	____	____
- Do chores such as vacuuming or yardwork?	____	____	____	____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

____Raised toilet seat
____Bathtub seat
____Jar opener (for jars previously opened)
____Bathtub bar
____Long-handled appliances for reach
____Long-handled appliances in bathroom
____Other (Specify: _____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

____Hygiene
____Reach
____Gripping and opening things
____Errands and chores

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A VERTICAL (I) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN.

NO PAIN 0 _____ SEVERE PAIN 100

HAQ-DI – United States/English
HAQ-DI_AU1.0-eng-USorl.doc

10.8.6. Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI)

Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) *ver02*

Select the score in each anatomical location that describes the most severely affected dermatomyositis-associated skin lesion

Extent

	activity			damage		
Anatomical Location	Erythema	Scale	Erosion/ Ulceration	Poikiloderma (Dyspigmentation or Telangiectasia)	Calcinosis	Anatomical Location
	0-absent 1-pink; faint erythema 2-red 3-dark red	0-absent 1-scale 2-crust; lichenification	0-absent 1-present	0-absent 1-present	0-absent 1-present	
Scalp						Scalp
Malar Area						Malar Area
Periorbital						Periorbital
Rest of the face						Rest of the face
V-area neck (frontal)						V-area neck (frontal)
Posterior Neck						Posterior Neck
Upper Back & Shoulders						Upper Back & Shoulders
Rest of Back & Buttocks						Rest of Back & Buttocks
Abdomen						Abdomen
Lateral Upper Thigh						Lateral Upper Thigh
Rest of Leg & Feet						Rest of Leg & Feet
Arm						Arm
Mechanic's Hand						Mechanic's Hand
Dorsum of Hands (not over joints)						Dorsum of Hands (not over joints)
Gottron's – Not on Hands						Gottron's – Not on Hands

Gottron's – Hands

Examine patient's hands and double score if papules are present		Ulceration	Examine patient's hands and score if damage is present	
0-absent 1-pink; faint erythema 2-red erythema 3-dark red			0-absent 1-dyspigmentation 2-scarring	

Periungual

Periungual changes (examine)			
0-absent 1-pink/red erythema/microscopic telangiectasias 2-visible telangiectasias			

Alopecia

Recent Hair loss (within last 30 days as reported by patient)			
0-absent 1-present			

Total Activity Score		Total Damage Score	
(For the activity score, please add up the scores of the left side, i.e. Erythema, Scale, Excoriation, Ulceration, Gottron's, Periungual, Alopecia)		(For the damage score, add up the scores of the right side, i.e. Poikiloderma, Calcinosis)	

10.8.7. Cutaneous Dermatomyositis Activity Physician's Global Assessment (CDA-IGA)

Cutaneous Dermatomyositis Activity Physician's Global Assessment (CDA-IGA)	
0- Clear	**Erythema** - none **Scale** - none **Secondary Change**: no lichenification **Secondary Changes:** no erosions, ulcers
1- Almost clear	**Erythema** – faint **Scale** - minimal **Secondary Change:** No lichenification **Secondary Changes:** no erosions, ulcers
2- Mild	**Erythema** – pink/mild **Scale** – fine, patchy **Secondary Change:** mild lichenification **Secondary Changes:** mild superficial erosion, no ulcers
3- Moderate	**Erythema** - red erythema **Scale** – thick, patchy **Secondary Change:** moderate lichenification **Secondary Changes:** moderate, superficial erosion or superficial ulcers present
4- Severe	**Erythema** – violaceous/bright red erythema **Scale** – thick, confluent **Secondary Change:** Extensive lichenification **Secondary Changes:** Marked erosion, deep ulcers present

Instructions:

Severity is determined by a combination of 2 characteristics (erythema, scale), and secondary changes based on descriptions of each characteristic.

Erythema is the PRIMARY characteristic that should influence the rating, with scale, and secondary characteristics considered given less importance Telangiectatic or pigmentation change should NOT be considered.

Assessment does NOT require all four characteristics to be present.

Severity of the morphologic features **are AVERAGED over the burden of lesions.**

Other Notes:
Anchored to photographic teaching / investigator education teaching set.

10.8.8. EuroQoL 5 Dimensions (EQ-5D-5L)

10.8.8.1. EQ-5D-5L Version for In-Clinic Use

Header to be completed by Study Site

Study Number: Subject ID: _____

Date Completed: _____ Time Completed: _____

Completed by: ☐ Patient

Health Questionnaire

English version for the USA

EQ-5D-5L Version for In-Clinic Use (Continued)

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

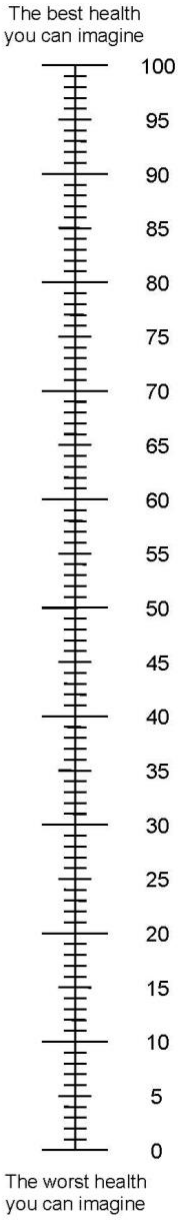
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

EQ-5D-5L Version for In-Clinic Use (Continued)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

10.8.9. 5D-Itch Scale

5-D Pruritus Scale

1. **Duration:** During the last 2 weeks, how many hours a day have you been itching?

Less than 6hrs/day	6-12 hrs/day	12-18 hrs/day	18-23 hrs/day	All day
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Degree:** Please rate the intensity of your itching over the past 2 weeks

Not present	Mild	Moderate	Severe	Unbearable
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **Direction:** Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting worse
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **Disability:** Rate the impact of your itching on the following activities over the last 2 weeks

	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
Sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
Leisure/Social	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Housework/ Errands	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Work/School	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **Distribution:** Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

	Present		Present
Head/Scalp	☐	Soles	☐
Face	☐	Palms	☐
Chest	☐	Tops of Hands/Fingers	☐
Abdomen	☐	Forearms	☐
Back	☐	Upper Arms	☐
Buttocks	☐	Points of Contact w/ Clothing	
Thighs	☐	(e.g waistband, undergarment)	☐
Lower legs	☐	Groin	☐
Tops of Feet/Toes	☐		

10.8.10. PROMIS-29 v2.1 Tool

PROMIS–29 Profile v2.1

Please respond to each question or statement by marking one box per row.

	Physical Function	Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

07 February 2018
 Page 1 of 3

PROMIS–29 Profile v2.1

	Fatigue **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
FATEXP41	How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Sleep Disturbance **In the past 7 days…**	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep116	My sleep was refreshing.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Ability to Participate in Social Roles and Activities	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
SRPPER11_CaPS	I have trouble doing all of my regular leisure activities with others.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER46_CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ9	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ21	How much did pain interfere with your ability to participate in social activities? .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

07 February 2018
 Page 2 of 3

PROMIS–29 Profile v2.1

Pain Intensity

In the past 7 days…

Global07	How would you rate your pain on average?.....	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst pain imaginable**

 Page 3 of 3

10.8.11. Short Form Health Survey (36 Questions Version) (SF-36)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SF-36 (Continued)

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h. Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i. Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

SF-36 (Continued)

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SF-36 (Continued)

6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SF-36 (Continued)

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SF-36 (Continued)

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

10.8.12. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

16 November 2007
Page 1 of 1

10.8.13. Dermatomyositis Disease Symptoms Questionnaire (DM-DSQ) v1.1 and v5.0

DM-DSQ pilot v1.1

DM-DSQ

Dermatomyositis – Disease Symptom Questionnaire

Please choose the response below that best describes the severity of each symptom over the past 24 hours.

Muscle weakness	None	Mild	Moderate	Severe	Very severe
Muscle stiffness	None	Mild	Moderate	Severe	Very severe
Muscle pain	None	Mild	Moderate	Severe	Very severe
Muscle burning	None	Mild	Moderate	Severe	Very severe
Muscle spasm	None	Mild	Moderate	Severe	Very severe
Joint pain	None	Mild	Moderate	Severe	Very severe
Skin rash	None	Mild	Moderate	Severe	Very severe
Skin itchiness	None	Mild	Moderate	Severe	Very severe
Skin sensitivity in sunlight	None	Mild	Moderate	Severe	Very severe
Fatigue	None	Mild	Moderate	Severe	Very severe
Slowness of movement	None	Mild	Moderate	Severe	Very severe
Difficulty swallowing	None	Mild	Moderate	Severe	Very severe
Difficulty breathing	None	Mild	Moderate	Severe	Very severe
Thickened, dry, or cracked skin on fingers or palms; appear rough or dirty	None	Mild	Moderate	Severe	Very severe

How has your DM been in the past 24 hours?

Not at all active	Mildly active	Moderately active	Very active	Extremely active

DM-DSQ 5.0

Dermatomyositis – Disease Symptom Questionnaire

Please circle (paper version) or select (electronic version) the response below that best describes the severity of each symptom over the past 7 days.

1 Muscle weakness	None 1	Mild 2	Moderate 3	Severe 4	Very severe 5
2 Muscle stiffness	None 1	Mild 2	Moderate 3	Severe 4	Very severe 5
3 Muscle pain	None 1	Mild 2	Moderate 3	Severe 4	Very severe 5
4 Muscle burning	None 1	Mild 2	Moderate 3	Severe 4	Very severe 5
5 Muscle soreness	None 1	Mild 2	Moderate 3	Severe 4	Very severe 5
6 Muscle cramping	None 1	Mild 2	Moderate 3	Severe 4	Very severe 5
7 Joint pain	None 1	Mild 2	Moderate 3	Severe 4	Very severe 5
8 Skin rash	None 1	Mild 2	Moderate 3	Severe 4	Very severe 5
9 Skin itchiness	None 1	Mild 2	Moderate 3	Severe 4	Very severe 5
10 Skin painful to touch	None 1	Mild 2	Moderate 3	Severe 4	Very severe 5
11 Fatigue	None 1	Mild 2	Moderate 3	Severe 4	Very severe 5
12 Tiredness	None 1	Mild 2	Moderate 3	Severe 4	Very severe 5
13 Muscle fatigability (muscles get tired after activity)	None 1	Mild 2	Moderate 3	Severe 4	Very severe 5
14 Slowness of movement	None 1	Mild 2	Moderate 3	Severe 4	Very severe 5
15 Difficulty swallowing	None 1	Mild 2	Moderate 3	Severe 4	Very severe 5
16 Difficulty breathing	None 1	Mild 2	Moderate 3	Severe 4	Very severe 5
17 Thickened, dry, or cracked skin on fingers or palms; appear rough or dirty	None 1	Mild 2	Moderate 3	Severe 4	Very severe 5

18 PGI-S for administration at all timepoints

A. Please circle (paper version) or select (electronic version) the response below that best describes the overall severity of your DM **SKIN** symptoms over the past 7 days.

None	Mild	Moderate	Severe	Very severe
1	2	3	4	5

B. Please circle (paper version) or select (electronic version) the response below that best describes the overall severity of your DM **MUSCLE** symptoms over the past 7 days.

None	Mild	Moderate	Severe	Very severe
1	2	3	4	5

C. Please circle (paper version) or select (electronic version) the response below that best describes the **OVERALL** severity of your DM symptoms over the past 7 days.

None	Mild	Moderate	Severe	Very severe
1	2	3	4	5

19 DM Activity for administration at all timepoints

A. How **active has** your DM been in the past 7 days? Please circle (paper version) or select (electronic version) your response.

Not at all active	Mildly active	Moderately active	Very active	Extremely active
1	2	3	4	5

20 PGI-C for administration at 1 week, 4 weeks, 3 months, and 6 months

A. Please circle (paper version) or select (electronic version) the response below that best describes the overall change in your DM **SKIN** symptoms compared to before you started taking the study medication.

Much improved	Moderately improved	A little improved	No change	A little worse	Moderately worse	Much worse

B. Please circle (paper version) or select (electronic version) the response below that best describes the overall change in your DM **MUSCLE** symptoms compared to before you started taking the study medication.

Much improved	Moderately improved	A little improved	No change	A little worse	Moderately worse	Much worse

C. Please circle (paper version) or select (electronic version) the response below that best describes the **OVERALL** change in your DM symptoms compared to before you started taking the study medication.

Much improved	Moderately improved	A little improved	No change	A little worse	Moderately worse	Much worse

10.8.14. 30-Second Chair Stand

ASSESSMENT

30-Second Chair Stand

Purpose: To test leg strength and endurance

Equipment: A chair with a straight back without arm rests (seat 17" high), and a stopwatch.

① Instruct the patient:

1. Sit in the middle of the chair.
2. Place your hands on the opposite shoulder crossed, at the wrists.
3. Keep your feet flat on the floor.
4. Keep your back straight, and keep your arms against your chest.
5. On "Go," rise to a full standing position, then sit back down again.
6. Repeat this for 30 seconds.

NOTE: Stand next to the patient for safety.

② On the word "Go," begin timing.

If the patient must use his/her arms to stand, stop the test. Record "0" for the number and score.

③ Count the number of times the patient comes to a full standing position in 30 seconds.

If the patient is over halfway to a standing position when 30 seconds have elapsed, count it as a stand.

④ Record the number of times the patient stands in 30 seconds.

Number: _____ Score: _____

Patient _____

Date _____

Time _____ ☐ AM ☐ PM

SCORING

Chair Stand
Below Average Scores

AGE	MEN	WOMEN
60-64	< 14	< 12
65-69	< 12	< 11
70-74	< 12	< 10
75-79	< 11	< 10
80-84	< 10	< 9
85-89	< 8	< 8
90-94	< 7	< 4

A below average score indicates a risk for falls.

CDC's STEADI tools and resources can help you screen, assess, and intervene to reduce your patient's fall risk. For more information, visit www.cdc.gov/steadi

Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

2017

STEADI Stopping Elderly Accidents, Deaths & Injuries

10.9. COVID-19 Risk Assessment

DM can cause irreversible morbidity and even mortality, if untreated. As such, and due to the limited number of available treatment options, the benefit a participant may receive from joining an investigational study with a therapeutic treatment is potentially significant. Given that treatment for DM does involve immunosuppression, there is a theoretical concern that the risk for infection may be higher than in participants not receiving immunosuppressants. However, there is no specific data to further inform this risk. The site Investigator will therefore balance the risk/benefit considerations in the study participant taking these factors into account.

The potential risks identified and mitigation measures put in place in light of the COVID-19 pandemic are provided in Table 20.

Table 20: Potential Risks and Mitigation Measures Due to COVID-19

Risks Category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
Healthcare institution availability for non-COVID-19-related activities	COVID-19 pandemic may impact the workload of healthcare institutions globally and may reduce staff availability to perform non-urgent activities and non-COVID-19-related activities.	During the time that the COVID19 pandemic is active, Alexion will only open study sites that report enough personnel capacity to sufficiently conduct clinical study related activities.
Data quality and integrity	Lack of availability of site personnel to perform study assessments and capture study specific data in a timely manner and to maintain adequate quality standards. Lack of availability of site personnel to ensure adequate and continuous chain of custody, storage conditions, and monitoring for investigational product and biological samples. Inability of study monitors and quality personnel to conduct in-person visits to exercise adequate oversight of study execution at investigational sites. Missing data (COVID19 pandemic may impact study visit schedules and increase missed visits and/or participant study discontinuations inadvertently resulting in missing data [eg, for protocol-specified procedures]).	During the time that the COVID19 pandemic is active, Alexion will only open study sites that report enough personnel capacity to sufficiently conduct clinical study related activities. During this timeframe, participants eligibility as well as site capacity will be reviewed by the site Investigator and the Alexion Medical Monitor or designee prior to Screening. Each site is also evaluated for the capacity to perform remote monitoring visits and remote source data verification. During the time that the COVID-19 pandemic is active, it will be important to capture specific information in the eCRF that explains the reason the data

Table 20: Potential Risks and Mitigation Measures Due to COVID-19

Risks Category	Summary of Data/ Rationale for Risk	Mitigation Strategy
		are missing (eg, missed study visits or participant study discontinuations due to COVID-19).

Abbreviations: COVID-19 = coronavirus disease 2019; eCRF = electronic case report form

10.10. COVID-19 Vaccine Risk Assessment

Following a review of the available COVID-19 vaccine data (eg, Pfizer/BioNTech, Moderna, AstraZeneca, Johnson & Johnson), it is unlikely that the immune response to a COVID-19 vaccine (and therefore the efficacy of the vaccination) would be diminished with concomitant ravulizumab administration, based on ravulizumab's mechanism of action. There is currently no information available evaluating the safety and efficacy of COVID-19 vaccines in participants treated with ravulizumab.

Vaccination may further activate complement. As a result, participants with complement-mediated diseases may experience increased signs and symptoms of their underlying disease. Therefore, participants should be closely monitored for disease symptoms after recommended vaccination.

Because vaccines may activate complement, if possible, consider vaccination when the underlying complement-mediated disease is clinically controlled and when systemic C5 inhibitor concentration (and subsequent complement blockade) is relatively high, shortly after administration.

Local and national guidelines should be consulted for recommendations related to COVID-19 vaccination.

The potential risks identified and mitigation measures put in place in light of the COVID-19 vaccination rollout are provided in Table 21.

Table 21: Potential Risks and Mitigation Measures Due to COVID-19 Vaccine

Risks Category	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential risks		
Data quality and integrity	Missing data due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine may impact study visit schedules and increase missed visits and/or participant study discontinuations, inadvertently resulting in missing data (eg, for protocol-specified procedures).	Capture specific information in the eCRF that explains the reason the data is missing (eg, missed study visits due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine).

Abbreviations: COVID-19 = coronavirus disease 2019; eCRF = electronic case report form

10.11. Abbreviations

The following abbreviations and terms are used in this study protocol.

Table 22: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
30s CST	30-second Chair Stand Test
ACR	American College of Rheumatology
ADA	antidrug antibody
AE	adverse event
AESI	adverse events of special interest
aHUS	atypical hemolytic uremic syndrome
ALT	alanine aminotransferase
anti-MDA5	antimelanoma differentiation-associated protein 5
anti-NXP2/MJ	antinuclear matrix protein 2
AST	aspartate aminotransferase
C3	complement component 3
C5	complement component 5
C5a	complement component 5a
C5b	complement component 5b
C5b-9	terminal complement complex
CDA-IGA	Cutaneous Dermatomyositis Activity Physician's Global Assessment
CDASI	Cutaneous Dermatomyositis Disease Area and Severity Index
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
COVID-19	coronavirus disease 2019
CRF	case report form
CSM	core set measure
CTCAE	Common Terminology Criteria for Adverse Events
DM	dermatomyositis
DMC	Data Monitoring Committee
DM-DSQ	Dermatomyositis Disease Symptoms Questionnaire

Table 22: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study
ePRO	electronic patient-reported outcome
EQ-5D-5L	European Quality of Life Health 5-item questionnaire dimensions 5 level
ET	Early Termination
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GPS	Global Patient Safety
gMG	generalized myasthenia gravis
HAQ	Health Assessment Questionnaire
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMACS	International Myositis Assessment and Clinical Studies
IMACS-TIS	International Myositis Assessment and Clinical Studies Total Improvement Score
IRB	Institutional Review Board
IRT	interactive response technology

Table 22: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
IST	immunosuppressive/immunomodulatory therapy
IV	intravenous(ly)
IVIg	intravenous immunoglobulin
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MAC	membrane attack complex
MDAAT	Myositis Disease Activity Assessment Tool
MedDRA	Medical Dictionary for Regulatory Activities
MITAX	Myositis Intention to Treat Activities Index
MMT-8	manual muscle testing subset of 8 muscles
MRI	magnetic resonance imaging
MYOACT	Myositis Disease Activity Assessment VAS
NMOSD	neuromyelitis optica spectrum disorder
NSAID	non-steroidal anti-inflammatory drug
OLE	Open-Label Extension
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PPS	Per Protocol Set
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	physical therapy
q8w	every 8 weeks
RCP	Randomized Controlled Period
SAE	serious adverse events
SAP	Statistical Analysis Plan
SC	subcutaneous
SF-36	Short Form Health Survey (36 questions version)
SLE	systemic lupus erythematosus
SoA	Schedule of Activities
SOC	System Organ Class

Table 22: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
SS	Safety Set
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TIS	total improvement score
TIS20	≥ 20-point improvement response on IMACS-TIS
TIS40	≥ 40-point improvement response on IMACS-TIS
TIS60	≥ 60-point improvement response on IMACS-TIS
ULN	upper limit of normal
VAS	visual analog scale
wGEE	weighted generalized estimating equation
WOCBP	woman of childbearing potential

10.12. Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the Table of Contents.

DOCUMENT HISTORY			
Document	**Type of Amendment (Global or Country-specific)**	**Date**	**Summary of Key Changes in the Amendment**
Amendment 2.0	Global	30 Aug 2022	To broaden the target population, reduce the risk of screen failures, improve patient experience, and to facilitate recruitment of participants.
Amendment 1.0	Global	27 Aug 2021	To provide information on the IDMC, a clarification on Part A interim analysis, individual and study closure criteria.
Amendment 0.2	UK	10 Aug 2021	To provide information regarding the IDMC, and to clarify interim analysis
Amendment 0.1	Germany	11 Aug 2021	To introduce an IDMC and update study closure criteria
Original protocol	Not applicable	07 May 2021	Not applicable

11. REFERENCES

Agarwal S, Kiely PD. Two simple, reliable and valid tests of proximal muscle function, and their application to the management of idiopathic inflammatory myositis. Rheumatology (Oxford). 2006;45(7):874-879.

Aggarwal R, Rider LG, Ruperto N, et al. 2016 American College of Rheumatology/European League Against Rheumatism Criteria for Minimal, Moderate, and Major Clinical Response in Adult Dermatomyositis and Polymyositis: An International Myositis Assessment and Clinical Studies Group/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Arthritis Rheumatol. 2017;69(5):898-910.

Bendewald MJ, Wetter DA, Li X, Davis MD. Incidence of dermatomyositis and clinically amyopathic dermatomyositis: a population-based study in Olmsted County, Minnesota. Arch Dermatol. 2010;146(1):26-30.

Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975;292(7):344-347.

Casadevall N, Nataf J, Viron B, et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. N Engl J Med. 2002;346(7):469-475.

Chan IS, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics. 1999;55(4):1202-1209.

Chandra T, Aggarwal R. Clinical trials and novel therapeutics in dermatomyositis. Expert Opin Emerg Drugs. 2020:1-16.

Dalakas MC. Review: An update on inflammatory and autoimmune myopathies. Neuropathol Appl Neurobiol. 2011;37(3):226-242.

Dalakas MC. Inflammatory muscle diseases. N Engl J Med. 2015;372(18):1734-1747.

Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. Lancet. 2003;362(9388):971-982.

Dalakas MC, Alexopoulos H, Spaeth PJ. Complement in neurological disorders and emerging complement-targeted therapeutics. Nat Rev Neurol. 2020;16(11):601-617.

Ernste FC, Reed AM. Idiopathic inflammatory myopathies: current trends in pathogenesis, clinical features, and up-to-date treatment recommendations. Mayo Clin Proc. 2013;88(1):83-105.

Howard JF, Jr., Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. Lancet Neurol. 2017;16(12):976-986.

Isak V, Jorizzo JL. Recent developments on treatment strategies and the prognosis of dermatomyositis: a review. J Dermatolog Treat. 2018;29(5):450-459.

Kissel JT, Mendell JR, Rammohan KW. Microvascular deposition of complement membrane attack complex in dermatomyositis. N Engl J Med. 1986;314(6):329-334.

Kronzer VL, Kimbrough BA, Crowson CS, Davis JM, 3rd, Holmqvist M, Ernste FC. Incidence, prevalence, and mortality of dermatomyositis: a population-based cohort study. Arthritis Care Res (Hoboken). 2021.

Lahoria R, Selcen D, Engel AG. Microvascular alterations and the role of complement in dermatomyositis. Brain. 2016;139(Pt 7):1891-1903.

Li J, Yang C, Xia Y, et al. Thrombocytopenia caused by the development of antibodies to thrombopoietin. Blood. 2001;98(12):3241-3248.

Lundberg IE, Tjarnlund A, Bottai M, et al. 2017 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies and Their Major Subgroups. Arthritis Rheumatol. 2017;69(12):2271-2282.

Magro CM, Crowson AN. The immunofluorescent profile of dermatomyositis: a comparative study with lupus erythematosus. J Cutan Pathol. 1997;24(9):543-552.

Mahil S, Marks D, McCormack M, Rahman A. Dermatomyositis. Br J Hosp Med (Lond). 2012;73(2):C18-22.

Marie I, Hachulla E, Hatron PY, et al. Polymyositis and dermatomyositis: short term and longterm outcome, and predictive factors of prognosis. J Rheumatol. 2001;28(10):2230-2237.

Matis LA, Rollins SA. Complement-specific antibodies: designing novel anti-inflammatories. Nat Med. 1995;1(8):839-842.

Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Stat Med. 2011;30(28):3267-3284.

Muppidi S, Utsugisawa K, Benatar M, et al. Long-term safety and efficacy of eculizumab in generalized myasthenia gravis. Muscle Nerve. 2019;60(1):14-24.

Pinal-Fernandez I, Casciola-Rosen LA, Christopher-Stine L, Corse AM, Mammen AL. The Prevalence of Individual Histopathologic Features Varies according to Autoantibody Status in Muscle Biopsies from Patients with Dermatomyositis. J Rheumatol. 2015;42(8):1448-1454.

Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in aquaporin-4–positive neuromyelitis optica spectrum disorder. N Engl J Med. 2019;381(7):614-625.

Rider LG, Miller FW. Deciphering the clinical presentations, pathogenesis, and treatment of the idiopathic inflammatory myopathies. JAMA. 2011a;305(2):183-190.

Rider LG, Aggarwal R, Machado PM, et al. Update on outcome assessment in myositis. Nat Rev Rheumatol. 2018;14(5):303-318.

Rider LG, Werth VP, Huber AM, et al. Measures of adult and juvenile dermatomyositis, polymyositis, and inclusion body myositis: Physician and Patient/Parent Global Activity, Manual Muscle Testing (MMT), Health Assessment Questionnaire (HAQ)/Childhood Health Assessment Questionnaire (C-HAQ), Childhood Myositis Assessment Scale (CMAS), Myositis Disease Activity Assessment Tool (MDAAT), Disease Activity Score (DAS), Short Form 36 (SF-36), Child Health Questionnaire (CHQ), physician global damage, Myositis Damage Index (MDI), Quantitative Muscle Testing (QMT), Myositis Functional Index-2 (FI-2), Myositis Activities Profile (MAP), Inclusion Body Myositis Functional Rating Scale (IBMFRS), Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), Cutaneous Assessment Tool (CAT), Dermatomyositis Skin Severity Index (DSSI), Skindex, and Dermatology Life Quality Index (DLQI). Arthritis Care Res (Hoboken). 2011b;63 Suppl 11:S118-157.

Sallum AM, Kiss MH, Silva CA, et al. Difference in adhesion molecule expression (ICAM-1 and VCAM-1) in juvenile and adult dermatomyositis, polymyositis and inclusion body myositis. Autoimmun Rev. 2006;5(2):93-100.

Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-397.

Schrag A, Selai C, Jahanshahi M, Quinn NP. The EQ-5D--a generic quality of life measure-is a useful instrument to measure quality of life in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 2000;69(1):67-73.

Selva-O'Callaghan A, Pinal-Fernandez I, Trallero-Araguas E, Milisenda JC, Grau-Junyent JM, Mammen AL. Classification and management of adult inflammatory myopathies. Lancet Neurol. 2018;17(9):816-828.

Stewart AL, Hays RD, Ware JE, Jr. The MOS short-form general health survey. Reliability and validity in a patient population. Med Care. 1988;26(7):724-735.

Suarez-Calvet X, Gallardo E, Pinal-Fernandez I, et al. RIG-I expression in perifascicular myofibers is a reliable biomarker of dermatomyositis. Arthritis Res Ther. 2017;19(1):174.

Tegla CA, Cudrici C, Patel S, et al. Membrane attack by complement: the assembly and biology of terminal complement complexes. Immunol Res. 2011;51(1):45-60.

Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-483.