CLINICAL STUDY PROTOCOL

A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of IgPro20 (Subcutaneous Immunoglobulin, Hizentra®) in Adults with Dermatomyositis (DM) – The RECLAIIM Study

Study Number:	IgPro20_3007
Study Product:	IgPro20 (Hizentra®)
Development Phase:	Phase 3
Sponsor:	CSL Behring, LLC 1020 First Avenue King of Prussia, PA United States of America
Protocol Version:	Amendment 4
EudraCT Number:	2018-003171-35
IND Number:	18942
Protocol Date:	20 October 2022
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonisation), ethical principles that have their origin in the Declaration of Helsinki, and all applicable national and local regulations.

LIST OF PERSONNEL AND ORGANIZATIONS RESPONSIBLE FOR CONDUCT OF THE STUDY

A list of personnel and organizations responsible for the conduct of the study will be supplied to study sites as part of the Investigator's Study File. This list will be updated by CSL Behring (or delegate) and provided to the study sites as needed.

REVISION HISTORY

Date	Version	Summary of Changes
07 March 2019	Original	Not applicable
07 June 2019	Amendment 1	• Modification of study title • Addition of text regarding identified risk of TEE in treatment population, including new exclusion criteria, monitoring, Adverse Events of Special Interest, and study stopping rules • Addition of details regarding oral corticosteroid treatment, rescue, taper, and monitoring • Addition of key secondary endpoint for reduction of concomitant corticosteroid • Addition and clarification of objective disease measures for eligibility and stratification • Definition of clinically relevant improvement • Addition of monitoring for hemolysis • Addition of rationale of PK timing and addition of PK sample • Minor corrections, clarifications, and administrative changes including the addition of a Weight-based Dosing Regimen table

05 February 2020	Amendment 2	• Clarification of Exclusion Criteria 1 and 2 • Modification of definition of clinically relevant improvement • Deletion of permitted training on the infusion device at home • Removal of Definition of Worsening (DOW) assessments from Week 29 to End of Study (EOS) • Modification of list of autoantibody testing • Addition of allowance for drawing PK samples at home • Addition of specific reasons for which investigational medicinal product (IMP) must be discontinued • Clarification to the DOW and oral rescue corticosteroid treatment • Clarification to the concomitant oral corticosteroid tapering guidelines • Modification of acceptable methods of contraception • Modification to monitoring for thromboembolic events (TEEs) • Addition of detail about hemolysis grading • Update to the approximate volume of blood drawn from each subject • Addition of analysis sets • Minor corrections and clarifications, including word modifications and administrative changes

21 July 2020	Amendment 3	• Addition of Study Period 3 to assess the safety and efficacy of long-term treatment with IgPro20 for DM. • Addition of safety, efficacy, and exploratory endpoints associated with the addition of Study Period 3 • Modified stopping rules and monitoring related to TEEs • Adjusted language in blinding procedures to account for Period 3 • Added detail to contraindications • Clarified lifestyle restrictions with relation to physiotherapy • Adjusted the Study Procedures and Visit Schedule for Study Period 3 • Adjusted language for blood and PK sample collection • Minor corrections and clarifications, including word modifications and administrative changes

20 Oct 2022	Amendment 4	1. Updated Screening assessments 2. Clarified the previous "primary analysis" designation as either "primary data analysis" or "primary endpoint analysis" 3. Defined that 3 data analyses will be performed, and defined the EOP1 analysis as the primary data analysis 4. Removed references to which data are intended to be used for marketing authorization application 5. Updated study unblinding procedures 6. Clarified conditions of concomitant oral corticosteroid taper after Week 17 7. Specified that doses of stable concomitant medication may be decreased during Study Period 3 based on subject status 8. Clarified definitions for reference visits and end of period 9. Clarified statistical methods 10. Corrected minor errors concerning statistical analyses 11. Updated the weight-based dosing regimen table 12. Updated that rate of TEAEs per time at risk will be calculated instead of TEAEs per days with infusion 13. Update primary and key secondary estimands and statistical methods to account for intercurrent events of withdrawals related to the Ukraine war and add a sensitivity analysis for the primary estimand. 14. Extend the study open-label period, Study Period 3, until CCI months CCI [redacted] for the indication Dermatomyositis, whichever comes first

Clinical Study Protocol Synopsis

Title	A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of IgPro20 (Subcutaneous Immunoglobulin, Hizentra®) in Adults with Dermatomyositis (DM) – **The RECLAIIM Study**
Study Number	IgPro20_3007
Sponsor	CSL Behring (CSLB)
Development Phase	Phase 3
Study Product	IgPro20 (Hizentra®)
Indication	Dermatomyositis
Study Summary and Overview	This is a phase 3, multicenter, randomized, placebo-controlled, double-blind study of IgPro20 (subcutaneous immunoglobulin G [SCIG]) treatment in adult subjects with dermatomyositis (DM) with or without muscle weakness. After Screening, subjects will be randomized to 1 of 2 treatment sequences: **Sequence A**: 0.5 g/kg IgPro20 for 24 weeks (Study Period 1) followed by 0.5 g/kg IgPro20 for 28 weeks (Study Period 2) - OR - **Sequence B**: placebo for 24 weeks (Study Period 1) followed by 0.5 g/kg IgPro20 for 28 weeks (Study Period 2) Subjects with demonstrated treatment benefit at the End of Study Period 2 (EOP2) (Total Improvement Score [TIS] ≥ 20 points at Week 49) will be eligible to continue long-term treatment with open-label IgPro20 until the end of the study in Study Period 3.
Primary Objective	The primary objective of this study is to assess the efficacy of IgPro20 0.5 g/kg weekly subcutaneous (SC) doses in comparison to placebo in adult subjects with DM, as measured by responder status based on the TIS assessments at Weeks 17, 21, and 25.
Primary Endpoint	The primary endpoint is the responder status based on the TIS assessments at Weeks 17, 21, and 25.

Secondary Objectives	The secondary objectives of the study are: • To assess the efficacy, with additional clinical outcome measures, of IgPro20 in comparison to placebo • To assess the safety of IgPro20 in comparison to placebo • To assess the safety and efficacy of IgPro20 at Week 53 • To assess the safety of IgPro20 after Week 53 to end of study participation
Key Secondary Endpoints	Key secondary endpoints of the study are: • TIS at Week 25 • Change from Baseline in Manual Muscle Testing (MMT-8) at Week 25 • Change from Baseline in Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) total activity score at Week 25 • Reduction of oral corticosteroid dose at Week 25
Secondary Endpoints	Additional secondary endpoints of the study are: • TIS from Week 5 to Week 53 • Individual core set measures (CSMs; except muscle enzyme), and CDASI from Baseline to Week 53 o Physician Global VAS o Patient Global VAS o MMT-8 o Health Assessment Questionnaire - Disability Index (HAQ-DI) o Extramuscular Global Assessment • Definition of Worsening from Baseline to Week 53 • Reduction of oral concomitant corticosteroid dose from Baseline to Week 53 • Use of rescue corticosteroid treatment from Baseline to Week 25 • Mobility, Self-care, and Usual Activities domains of EuroQoL 5-Dimension Questionnaire (EQ-5D-5L) from Baseline to Week 53 • Treatment-emergent adverse events (TEAEs)

Study Duration	After up to 2 months of Screening, the duration for an individual subject is expected to be 24 weeks in Study Period 1 and 28 weeks in Study Period 2. The maximum study duration in the open-label Study Period 3 will be approximately 7 years; however, subject participation will end if the drug becomes commercially available (see Section 3.7) or if there is no longer benefit from the study drug. For subjects not eligible to participate in Study Period 3, study duration will be up to 56 weeks (including the Follow-up Telephone Call).
Number of Subjects	A sufficient number of subjects will be screened in order to randomize approximately 126 subjects into the study.

Study Population and Criteria for Eligibility

Inclusion criteria:

- Capable of providing written informed consent by signing an informed consent form and willing and able to adhere to all protocol requirements
- Age ≥ 18 years
- **Diagnosis** of at least probable idiopathic inflammatory myopathies per European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) Classification Criteria: minimum aggregate score of 5.5 without muscle biopsy and 6.7 with muscle biopsy (historical muscle biopsy is acceptable) which includes confirmation of DM rash/skin manifestation (present or by history [historical skin biopsy is required for amyopathic DM subjects])
- **Disease activity** defined by:
  - Presence of DM rash/skin manifestation (eg, Gottron's papules/sign, heliotrope rash, periorbital edema, V sign, Shawl sign) at Screening Visit - OR -
  - One objective disease activity measure within 3 months before Baseline:
    i. Magnetic resonance imaging (MRI) scan showing active inflammation (edema) of a proximal skeletal muscle - OR -
    ii. Electromyogram showing acute changes such as spontaneous activity not explained by other disease - OR -
    iii. Muscle biopsy with perivascular or perimysial inflammation - OR -
    iv. Creatine kinase (CK) > 4 times the upper limit of normal (4 × ULN)
- **Disease severity** at Screening and Baseline defined by a minimum value of 2 cm on a 10-cm Physician Global Disease Activity Visual Analog Scale and:
  - MMT-8 ≤ 142 - OR -
  - CDASI total activity score ≥ 14
- Subject has failed previous DM treatment or is on DM treatment such as immunosuppressants and/or antimalarials on a stable dose ≥ 3 months before Baseline; and/or oral corticosteroids (≤ 20 mg/day prednisolone equivalent and/or topical) on a stable dose ≥ 1 month before Baseline

Exclusion criteria:

- Cancer-associated myositis, defined as the diagnosis of myositis within 2 years of the diagnosis of cancer
- Evidence of malignancies diagnosed within the previous 5 years

  ***Note**: Subjects with a history of carcinoma in situ of the cervix that has been excised and cured with ≥ 5 years since excision or subjects with documented history of treated basal or squamous cell skin cancer may be enrolled into the study.*
- Physician Global Damage Assessment ≥ 3 on a 5-point Likert scale where a score of 3 represents severe damage
- Clinically relevant improvement between Screening Visit and Baseline, defined by ≥ 2 cm improvement on a 10-cm Physician Global Disease Activity Assessment Visual Analog Scale
- Known or suspected hypersensitivity or other severe reactions to IgPro20 or to any of its excipients, or other immunoglobulins (Igs) or severe reactions to blood products
- Other significant medical conditions that could increase the risk to the subject, eg:
  - History of allogeneic bone marrow/stem cell transplant/solid organ transplant
  - Cardiac insufficiency (New York Heart Association Class III or IV) or unstable ischemic heart disease
  - Chronic kidney disease stage IV or V
  - Recent surgery requiring general anesthesia within the previous 4 weeks before Screening
  - Known hyperprolinemia type I or type II
  - Documented thrombophilic abnormalities including blood hyperviscosity, protein C or protein S deficiency, antithrombin-III deficiency, plasminogen deficiency, antiphospholipid antibodies, Factor V Leiden mutation, dysfibrinogenemia, or prothrombin G20210A mutation
  - History of documented thrombotic episode, eg, pulmonary embolism, deep vein thrombosis, myocardial infarction, or thromboembolic stroke at any time
  - More than 3 of the following specified risk factors for thromboembolic events (documented and current conditions) occurring concurrently: atrial fibrillation, coronary disease, diabetes mellitus, dyslipidemia,

hypertension, obesity (body mass index ≥ 30 kg/m^2), recent significant trauma and immobility (wheelchair-bound or bedridden)
    - Uncontrolled, severe, or rapidly progressive interstitial lung disease which will prevent the subject from successful participation in the study
    - Severe skin disease at planned infusion sites that would make SC infusions infeasible
    - Medical conditions whose symptoms and effects could alter protein catabolism and or IgG utilization (eg, protein-losing enteropathies, nephrotic syndrome, known immunoglobulin A [IgA] deficiency with antibodies to IgA)
- Other conditions which would prevent correct assessment or lead to impaired muscle strength (eg, other neurological disorders including, but not limited to, Parkinson's disease or severe musculoskeletal conditions like severe osteoarthritis or deformities)
- Laboratory exclusions at Screening:
    - Positive result for any of the following: human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV)
    - Creatinine > 1.5 × ULN or blood urea nitrogen (BUN) > 3 × ULN
- Any of the following therapies:
    - Within **1 month** before Baseline: intramuscular, intravenous, or intra-articular corticosteroids including adrenocorticotropic hormone (any dose), doses > 20 mg/day prednisolone equivalent (any route), or any change to physiotherapy
    - Within **2 months** before Baseline: IgG (Note: Subject may enroll < 2 months after stopping IgG therapy if clinical deterioration is experienced after withdrawal)
    - Within **3 months** before Baseline: plasma exchange or plasmapheresis
    - Within **6 months** before Baseline: cyclophosphamide or alkylating agents
    - Within **6 months or 5 half-lives** of the drug, whichever is longer, before Baseline: other biologic therapies including investigational agents
    - Within **9 months** before Baseline: rituximab or evidence of persistent B cell depletion after stopping therapy

	• Male subject or female subject of childbearing potential either not using or not willing to use a medically reliable method of contraception (see Section 7.4.2), not sexually abstinent during the study, or not surgically sterile before study enrollment • Pregnant or breastfeeding • Alcohol, drug, or medication abuse within 1 year of providing informed consent • Previously received investigational medicinal product (IMP) in this study or failed Screening more than 1 time in this study • Involved in the planning and/or conduct of the study (applies to CSLB staff, staff at the study site, and third-party vendors) Any issue that, in the opinion of the investigator, would render the subject unsuitable for participation in the study or unable to comply with study procedures, eg, inability to self-administer IMP or by aid through a caregiver
IMP Dose, Dosing Regimen and Administration	IgPro20 will comprise a liquid, ready-to-use 20% IgG solution stabilized with 250 mmol/L L-proline and 20 mg/L polysorbate 80. All IgPro20 will be administered by SC infusions as weekly doses. The total dose/volume of IgPro20 will be calculated on the basis of the body weight. The weekly SC infusions can be administered on 1, 2, 3, or 4 days per week.
Comparator Product, Dose, Dosing Regimen and Administration	The placebo product will comprise a 2% human albumin solution in 250 mmol/L L-proline and 20 mg/L polysorbate 80 manufactured from the licensed, pasteurized CSLB human albumin 5% final product. All placebo will be administered by SC infusions as weekly doses. The total volume of placebo will be calculated on the basis of the body weight and volume-matched to the 0.5 g/kg IgPro20 dose. The weekly SC infusions can be administered on 1, 2, 3, or 4 days per week.
Efficacy Assessments	Efficacy will be assessed using the 6 CSMs used to calculate TIS (Patient Global Activity Assessment, MMT-8, Health Assessment Questionnaire, Muscle Enzymes, Physician Global Disease Activity, and Extramuscular Global Assessment), CDASI, and Timed Up and Go.

Safety Assessments	Safety will be assessed through TEAE documentation, laboratory safety parameters, vital signs, and physical examination. Specific monitoring for corticosteroid treatment, thromboembolic events (including implementation of study stopping rules for treatment imbalance), and hemolysis will also be performed.
Pharmacokinetics	Serum samples for IgG level determination will be collected at Screening and specified study visits. Additional blood samples for rich pharmacokinetic sampling of IgG levels will be collected at Week 37 on up to 10 Japanese subjects and 30 non-Japanese subjects.
Pharmacodynamics	Not applicable.
Other Assessments	Patient reported outcomes including 5-Dimension Itch Score, EQ-5D-5L, Work Productivity and Activity Impairment Questionnaire: General Health, and Treatment Satisfaction Questionnaire for Medication-9 will be assessed.
Statistical Analyses	The study is designed as a superiority study. The sample size calculation is based on the hypothesis that IgPro20 will have a higher responder rate than placebo based on the TIS assessments at Weeks 17, 21, and 25. A responder is defined as a subject with a TIS $\geq$ 20 points at Week 25 and at least 1 of the previous scheduled visits (Week 17 or Week 21), who completes 24 weeks of randomized IMP treatment without the use of rescue corticosteroid treatment. Note: for subjects who discontinue from IMP or the study for reasons that are related to the Ukraine war before Week 25, a multiple imputation approach will be used for dealing with missing TIS values. For power simulation, it is assumed that 65% of subjects randomized to IgPro20 and 30% of subjects randomized to placebo have a TIS $\geq$ 20 points at Week 17. Further, it is assumed that for each subject, the response at Week 21 is conditional on the response at Week 17, and the response at Week 25 is conditional on the response at Week 21. Simulation shows a total of 126 subjects (63 subjects per arm) will be required for a power of 90% in 1-sided Fisher's exact test at a significance level of 0.025. Fisher's exact test is used in the power simulation as a close approximation to the exact logistic regression model in the primary endpoint analysis.

Schedules of Assessments

For information on the handling of study assessments and study procedure responsibilities by role, see Section 8.1.1 and Table 7.

Table 1 Schedule of Assessments for Screening

	≤ 2 months before Baseline[A]
Assessments	
Informed consent/IRT registration	X
Medical/surgical history and demographics	X
DM treatment history[B]	X
Inclusion [EULAR/ACR criteria]/exclusion criteria	X
CDASI	X
General physical examination, including height	X
12-lead ECG	X
Body weight	X
Vital signs[C]	X
Wells' Criteria	X
Laboratory collections:	
Serum hCG pregnancy test[D]	X
Serum IgG level	X
Hematology[E]	X
ABO blood group and Rh factor	X
Muscle Enzymes[F]	X
Other biochemistry[G]	X
Thrombophilic Abnormality Screen[H]	X
Coagulation[I]	X
ANA, MSA, and MAA[J]	X
Virology sample[K]	X
Adverse events	X
Concomitant therapies	X
Physiotherapy	X
Individual CSMs[L]	X
Physician Global Damage Assessment	X

ABO = blood group type A, type B, type AB, or type O; ALT = alanine aminotransferase; ANA = antinuclear antibody; AST = aspartate transaminase; BUN = blood urea nitrogen; CDASI = Cutaneous Dermatomyositis Disease Area and Severity Index; CK = creatine kinase; CSMs = Core Set Measures; DM = dermatomyositis; ECG = electrocardiogram; EULAR/ACR = European League Against Rheumatism/American College of Rheumatology; GGT = gamma-glutamyl transferase; HAQ = Health Assessment Questionnaire; HBV = hepatitis B virus; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IRT = interactive response technology; LDH = lactate dehydrogenase; MAA = myositis-associated antibodies; MMT-8 = Manual Muscle Testing of 8 muscle groups; MSA = myositis-specific antibodies; Rh = Rhesus; TIS = Total Improvement Score.

Notes for the Schedule of Assessments for Screening:

A. Screening may be up to 2 months. Re-screening once per subject will be permitted for failed eligibility other than DM diagnosis or disease activity.

B. DM treatment history including IgG, corticosteroid, and other treatment.

C. Vital sign assessments include supine systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature.

D. Serum hCG pregnancy test is to be completed for all premenopausal female subjects capable of becoming pregnant. This includes women on oral, injectable, or mechanical contraception and women whose partners have been vasectomized or have received or are utilizing mechanical contraceptive devices.

E. Hematology: hemoglobin, hematocrit, platelets, erythrocytes, leukocytes with differential counts (neutrophils, basophils, eosinophils, lymphocytes, monocytes).

F. Muscle enzymes: CK, LDH, AST, ALT, aldolase.

G. Other biochemistry: sodium, potassium, chloride, bicarbonate, BUN, glucose, GGT, alkaline phosphatase, creatinine.

H. Thrombophilic Abnormality Screen: protein C, protein S, antithrombin-III, lupus anticoagulant, cardiolipin antibodies, prothrombin G20210A mutation, Factor V Leiden mutation.

I. Coagulation: D-dimer.

J. MSA and MAA: anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-SRP, anti-Mi-2, anti-p155/140, anti-TIF-1γ, anti-MDA5, anti-NXP-2, anti-PM/Scl, anti-Ro-SSA, anti-Ku, anti-U1 RNP, anti-U3 RNP, anti-HMGCR, anti-SAE-1Ab.

K. HBV, HCV, and HIV.

L. The 6 CSMs used in the TIS calculation ([1] Physician Global Disease Activity, [2] Patient Global Activity Assessment, [3] MMT-8, [4] HAQ, [5] Muscle Enzyme, and [6] Extramuscular Global Assessment) will be assessed for eligibility, along with Physician Global Damage Assessment.

Table 2 Schedule of Assessments for Study Period 1 and Study Period 2

Study Year	Year 1[A]																	
Study Period	Study Period 1[B]									Study Period 2[B]								
Study Week	Base-line	W1	W2 ±3d	W5 ±3d	W9 ±3d	W13 ±3d	W17 ±3d	W21 ±3d	W25 EOP1 ±3d	W29 ±3d	W33 ±3d	W37 ±3d	W41 ±3d	W45 ±3d	W49 ±3d	W53[C] ±3d	W56 EOP2 ±3d	UNS
Assessments																		
Confirm eligibility[D]	X																	
Randomization	X																	
General physical exam[E]	X								X							X		
12-lead ECG[E]																X		
Body weight	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Waist circumference	X								X							X		
IMP assignment[E,F]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X[G]		X[X]
Vital signs[H]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Safety assessments[I]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Laboratory collections:																		
Urine hCG pregnancy test[J]	X			X	X	X	X	X	X	X	X	X	X	X	X	X		X
Serum exploratory biomarkers[E,K]	X			X	X		X	X	X			X			X	X		X
DNA exploratory biomarkers[L]	X																	
RNA exploratory biomarkers[E]	X			X					X							X		
Hematology[M]	X		X	X	X		X		X		X			X		X		X
$HbA1_c$	X								X							X		
Muscle enzymes[N]	X			X	X	X	X	X	X	X	X	X	X	X	X	X		X
Additional labs for hemolysis criteria[O]	X		X	X														
Other biochemistry[P]	X				X		X		X		X			X		X		X

Study Year	**Year 1[A]**																	
Study Period	**Study Period 1[B]**									**Study Period 2[B]**								**UNS**
Study Week	**Base -line**	**W1**	**W2 ±3d**	**W5 ±3d**	**W9 ±3d**	**W13 ±3d**	**W17 ±3d**	**W21 ±3d**	**W25 EOP1 ±3d**	**W29 ±3d**	**W33 ±3d**	**W37 ±3d**	**W41 ±3d**	**W45 ±3d**	**W49 ±3d**	**W53[C] ±3d**	**W56 EOP2 ±3d**	
Assessments																		
Coagulation[Q]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Serum IgG levels[E]	X		X	X	X		X	X	X			X			X	X		X
Rich PK sampling[E]												X[K]						
ANA, MSA, and MAA[E,R]									X							X		
Virology retention sample[E,S]	X															X		
IMP SC infusion[E,T,U]		X	X	X----------											X	X[G]		X[X]
Subject SC Infusion Diary review[E]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
AEs	X----------																X	X
Concomitant therapies	X----------																X	X
Change to physiotherapy[V]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
DOW[Y]				X	X	X	X	X	X							X		X
Assess for clinically relevant improvement[Z]	X						X	X	X	X	X	X	X	X	X			X
Individual CSMs[AA]	X			X	X	X	X	X	X	X	X	X	X	X	X	X		X
CDASI	X			X	X	X	X	X	X	X	X	X	X	X	X	X		X
5-D Itch Score	X				X		X		X		X		X			X		
Timed Up and Go	X				X		X		X		X		X			X		
EQ-5D-5L, WPAI-GH, and TSQM-9[E,BB]	X					X			X		X		X			X		
Review eligibility for open-label Study Period 3																X		

Study Year	Year 1[A]																	
Study Period	Study Period 1[B]									Study Period 2[B]								
Study Week	Base -line	W1	W2 ±3d	W5 ±3d	W9 ±3d	W13 ±3d	W17 ±3d	W21 ±3d	W25 EOP1 ±3d	W29 ±3d	W33 ±3d	W37 ±3d	W41 ±3d	W45 ±3d	W49 ±3d	W53[C] ±3d	W56 EOP2 ±3d	UNS
Assessments																		
Safety follow-up telephone call																	X[CC]	

5-D = 5-Dimension; AE = adverse event; ALT = alanine aminotransferase; ANA = antinuclear antibody; AST = aspartate transaminase; BUN = blood urea nitrogen; CDASI = Cutaneous Dermatomyositis Disease Area and Severity Index; CK = creatine kinase; CSMs = Core Set Measures; d = days, DAT = direct antiglobulin Test; DNA = deoxyribonucleic acid; DOW = Definition of Worsening; DVT = deep vein thrombosis; ECG = electrocardiogram; eCRF = electronic case report form; EOP1 = End of Study Period 1; EOP2 = End of Study Period 2; EQ-5D-5L = EuroQoL 5-Dimension Questionnaire; GGT = gamma-glutamyl transferase; HAQ = Health Assessment Questionnaire; $HbA1_c$ = glycated hemoglobin; hCG = human chorionic gonadotropin; IgG = immunoglobulin G; IMP = investigational medicinal product; LDH = lactate dehydrogenase; MAA = myositis-associated autoantibodies; MMT-8 = manual muscle testing of 8 muscle groups; MSA = myositis-specific autoantibodies; PE = pulmonary embolism; PK = pharmacokinetic; RNA = ribonucleic acid; SC = subcutaneous; TEE = thromboembolic event; TIS = Total Improvement Score; TSQM-9 = Abbreviated Treatment Satisfaction Questionnaire for Medication; UNS = Unscheduled Visit; VAS = visual analog scale; W = week; WPAI-GH = Work Productivity and Activity Impairment Questionnaire for General Health.

Notes for the Schedule of Assessments for Study Period 1 and Study Period 2:

A. After up to 2 months of Screening, the duration for an individual subject is expected to be 24 weeks in Study Period 1 and 28 weeks in Study Period 2. The maximum study duration in the open-label Study Period 3 may be approximately 7 years; however, subject participation will end if the drug becomes available or if there is no longer benefit from the study drug. For subjects not eligible to participate in Study Period 3, study duration will be up to 56 weeks (including the Follow-up Telephone Call).
B. Study Period 1 starts at the Baseline Visit and continues to Week 25. Baseline assessments must be completed before the Week 1 assessments. Study Period 2 starts after the assessments at the Week 25 Visit and continues through the Week 53 Visit for subjects who are eligible and continue long-term treatment with IgPro20 in Study Period 3, or through the Week 56 Telephone Visit (EOP2) for subjects whose study participation ends with Study Period 2.
C. For subjects who discontinue IMP early during participation in Study Period 1 or Study Period 2, all Week 53 assessments will be performed at the study visit where IMP treatment is discontinued instead of the assessments scheduled for that particular study visit.
D. Confirmation per Treating and Evaluating Physicians that no clinically relevant improvement has occurred since Screening and that the subject is still eligible for the study.
E. This study assessment will not be performed at any study visit after discontinuation of IMP treatment.
F. Additional IMP will be assigned at UNS Visit if the subject's weight has increased (> 2 kg), which will require a dose volume increase (see Appendix 15).
G. Only if subject is eligible for continuation of treatment in Study Period 3.
H. Vital sign assessments include supine systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature.
I. Safety assessments: Monitoring for corticosteroid treatment, monitoring for TEEs (including Wells' Criteria score for DVT and/or Wells' Criteria score for PE), monitoring for hemolysis at Week 2 and Week 5 only.
J. Urine hCG pregnancy test is to be completed for all premenopausal females capable of becoming pregnant. This includes women on oral, injectable, or mechanical contraception and women whose partners have been vasectomized or have received or are utilizing mechanical contraceptive devices.
K. Additional laboratory collection for Week 37 is located in Schedule of Assessments for Rich Pharmacokinetic Sampling.
L. Optional DNA blood samples for exploratory biomarkers.
M. Hematology: hemoglobin, hematocrit, platelets, erythrocytes, leukocytes with differential counts (neutrophils, basophils, eosinophils, lymphocytes, monocytes).
N. Muscle enzymes: CK, LDH, AST, ALT, aldolase.

O. Hemolysis: DAT, total bilirubin, direct bilirubin, indirect bilirubin, haptoglobin, reticulocytes, and peripheral blood smear to check for spherocytosis. Peripheral blood smear will be performed at Week 2 and Week 5 only.
P. Other biochemistry: sodium, potassium, chloride, bicarbonate, BUN, glucose, GGT, alkaline phosphatase, creatinine.
Q. Coagulation: D-dimer complex.
R. MSA and MAA: anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-SRP, anti-Mi-2, anti-p155/140, anti-TIF-1γ, anti-MDA5, anti-NXP-2, anti-PM/Scl, anti-Ro-SSA, anti-Ku, anti-U1 RNP, anti-U3 RNP, anti-HMGCR, anti-SAE-1Ab.
S. Retention samples at Baseline and Week 53/end of study participation. A virology retention sample should be obtained for all subjects who discontinue at any time during the study.
T. IMP SC infusions at Week 1 and Week 2 are to be administered only after the visit-specific assessments (except SC infusion diary review) are completed.
U. Training and supervised IMP SC infusions at the site on Week 1 and Week 2. If additional infusion training at the site is requested by the subject for Week 3 and/or Week 4, no other UNS Visit assessments are required to be performed. Week 3 and Week 4 additional infusion training will be documented in the eCRF. After training is completed, IMP will not be administered during subsequent study visits. For the remainder of their participation in the study, subjects will self-administer IMP at home.
V. Physiotherapy regimen may be modified starting at Week 17 if clinically relevant improvement is achieved.
W. Only if subject discontinues IMP treatment before Week 25.
X. IMP will only be administered at the site for unscheduled visits which occur at Week 3 or Week 4.
Y. See Section 5.3.1 for DOW criteria and corticosteroid rescue details (Week 9 to Week 25). DOW assessment at UNS Visit only if before Week 25.
Z. ≥ 2 cm improvement from Baseline on 10-cm Physician Global Disease Activity VAS.
AA. Six individual CSMs will be assessed during the study for TIS calculation: (1) Physician Global Disease Activity, (2) Patient Global Activity Assessment, (3) Manual Muscle Testing of 8 muscle groups (MMT-8), (4) HAQ, (5) Muscle Enzyme, and (6) Extramuscular Global Assessment.
BB. TSQM-9 is not performed at Baseline.
CC. The Week 56 Safety Follow-up Telephone Call will not be performed for subjects who discontinue IMP treatment before Week 53 but remain in the study for at least 1 subsequent study visit 4 weeks after IMP discontinuation or subjects who are eligible to continue treatment in Study Period 3.

Table 3 Schedule of Assessments for Open-label Study Period 3

	Subsequent Years (4-week cycles)				
Study Week	**Every 4 weeks**	**Every 24 weeks**	**End of Year**	**UNS**	**EOP3**
Time Window	**±7d**	**±7d**	**±7d**	**NA**	**±7d**
Assessments					
Urine hCG pregnancy test[B]		X	X	X	X
Physical examination			X		X
Vital signs[C]		X	X	X	X
Body weight	X	X	X	X	X
Virology retention sample					X
Hematology and biochemistry[D, E]			X	X	X
Efficacy assessments (4 individual CSMs)[F]		X	X	X	X
CDASI		X	X	X	X
EQ-5D-5L		X	X	X	X
IMP assignment[G]	X	X	X[H]		
IMP SC weekly infusions	X	X	X[H]		
Subject SC Infusion Diary Review	X	X	X	X	X
AEs	◄———	———	———	———	———►
Concomitant therapies	◄———	———	———	———	———►

AE = adverse event; BUN = blood urea nitrogen; CDASI = Cutaneous Dermatomyositis Disease Area and Severity Index; CSM = core set measure; d = day
EQ-5D-5L = EuroQoL 5-Dimension Questionnaire; EOP3 = End of Study Period 3; GGT = gamma-glutamyl transferase; HAQ= Health Assessment Questionnaire; hCG = human chorionic gonadotropin; IMP = investigational medicinal product; M = month; MMT-8 = Manual Muscle Testing of 8 muscle groups; NA = not applicable; SC = subcutaneous; UNS = unscheduled visit; W = week.

Notes for the Schedule of Assessments for Study Period 3:

A. For subjects who discontinue IMP during participation in Study Period 3, all EOP3 assessments will be performed at the study visit where subjects discontinue/end study participation.

B. A urine pregnancy test will be performed on all female subjects of childbearing potential.

C. Vital sign assessments include supine systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature.

D. Hematology: hemoglobin, hematocrit, platelets, erythrocytes, leukocytes with differential counts (neutrophils, basophils, eosinophils, lymphocytes, monocytes).
E. Biochemistry: sodium, potassium, chloride, bicarbonate, BUN, glucose, GGT, alkaline phosphatase, creatinine.
F. Four individual CSMs will be assessed in Study Period 3: Physician Global Disease Activity and Patient Global Activity Assessment, MMT-8, and HAQ.
G. Additional IMP will be assigned at UNS Visit if the subject's weight has increased (> 2 kg), which will require a dose volume increase (see Appendix 15).
H. IMP will be dispensed at this visit only if the subject is continuing in Study Period 3.

Table 4 Schedule of Assessments for Rich Pharmacokinetic Sampling

Study Week	**Week 37**				
Sampling Time[A]	+24 ± 3 h relative to the start of first infusion	+48 ± 3 h relative to the start of first infusion	+72 ± 3 h relative to the start of first infusion	+120 ± 3 h relative to the start of first infusion	+168 ± 3 h relative to the start of first infusion[C]
Serum for IgG levels[B]	X	X	X	X	X
Serum for exploratory biomarkers	X	X	X	X	X

h = hours; IgG = immunoglobulin G.

Notes to the schedule of assessments for Rich PK Sampling:

A. Blood draws for rich PK samples may be drawn by a phlebotomist at the subject's home where available and/or allowed by local law.
B. The Week 37 trough level sample will be drawn at the study visit before the start of the first Week 37 dose infusion at home.
C. The Week 37, 168-hour rich PK blood sample must be drawn before start of the first Week 38 dose infusion.

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List of Abbreviations

Abbreviation	Term
5-D	5-Dimension
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BDRM	Blinded Data Review Meeting
BUN	Blood urea nitrogen
C_{max}	Maximum concentration
C_{trough}	Trough concentration
CDASI	Cutaneous Dermatomyositis Disease Area and Severity Index
CI	Confidence interval
CIDP	Chronic inflammatory demyelinating polyneuropathy
CK	Creatine kinase
CRF	Case report form
CSLB	CSL Behring
CSM	Core set measure
CTA	Clinical trial application
CTN	Clinical trial notification
DAT	Direct antiglobulin test
DM	Dermatomyositis
DOW	Definition of Worsening
DVT	Deep vein thrombosis
eCOA	Electronic clinical outcomes assessment
ELISA	Enzyme-linked immunosorbent assay
EOP	End of Study Period
EOS	End of Study
EOT	End of Treatment
EQ-5D-5L	EuroQoL 5-Dimension Questionnaire
EULAR / ACR	European League Against Rheumatism/American College of Rheumatology
FDA	Food and Drug Administration
GCP	Good Clinical Practice

Abbreviation	Term
GMP	Good Manufacturing Practice
HAQ	Health Assessment Questionnaire
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
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
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IIM	Idiopathic inflammatory myopathies
IMACS	International Myositis Assessment and Clinical Studies
IM	Intramuscular
IMP	Investigational medicinal product
IND	Investigational new drug
IRB	Institutional Review Board
IRT	Interactive response technology
IV	Intravenous
IVIG	Intravenous immunoglobulin G
LDH	Lactate dehydrogenase
MAA	Myositis-associated autoantibodies
MDAAT	Myositis Disease Activity Assessment Tool
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat analysis set
mITT-Ex	modified Intent-to-Treat analysis set extended
MMRM	Mixed Model Repeated Measures
MMT-8	Manual Muscle Testing of 8 muscle groups
MRI	Magnetic resonance imaging
MSA	Myositis-specific autoantibodies
PE	Pulmonary embolism
PK	Pharmacokinetic analysis set
PM	Polymyositis

Abbreviation	Term
PP	Per Protocol analysis set
PT	Preferred term
SAE	Serious adverse event
SAF	Safety analysis set
SAF-Ex	Safety analysis set extended
SAP	Statistical analysis plan
SC	Subcutaneous
SCIG	Subcutaneous immunoglobulin G
SCR	Screened analysis set
SOC	System organ class
TEAE	Treatment-emergent Adverse Event
TEE	Thromboembolic event
TIS	Total Improvement Score
TSQM-9	Abbreviated Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal
VAS	Visual analog scale
WPAI-GH	Work Productivity and Activity Impairment Questionnaire for General Health

Glossary of Terms

Term	Definition
Baseline	Week 1, before infusion of investigational medicinal product (IMP)
DOW	The DOW consists of meeting 1 of the following 3 criteria on 2 consecutive study visits at least 2 weeks apart: • Physician Global Disease Activity Assessment VAS worsening ≥ 2 cm* and MMT-8 worsening ≥ absolute 10%, - OR - • Extramuscular Global Assessment VAS worsening ≥ 2 cm, - OR - • Any 3 of 6 CSMs (see Section 3.3.1) worsening by ≥ absolute 20% * If baseline Physician Global VAS is 8 to 10, then any worsening on Physician Global VAS is acceptable as long as MMT-8 criterion is met.
EOP	End of Study Period distinguishes periods 1, 2 and 3 of the study.
g/kg	IMP dose throughout the study will be calculated by gram/kg of body weight. For all dosing references in the protocol, the dose description is shortened to g/kg.
Primary data analysis	The primary data analysis (ie, EOP1 analysis) includes all data collected during Study Period 1.
Primary endpoint analysis	The primary endpoint analysis refers to the analysis of the primary objective, ie, the responder status based on the TIS assessments at Weeks 17, 21, and 25.
Responder	A subject with a TIS ≥ 20 points at Week 25 and at least 1 of the previous scheduled visits (Week 17 or Week 21), who completes 24 weeks of randomized IMP treatment (ie, Study Period 1) without the use of rescue corticosteroid treatment. Note: for subjects who discontinue from IMP or the study for reasons that are related to the Ukraine war before Week 25, a multiple imputation approach will be used for dealing with missing TIS values (see Section 10.4.2).
Study Treatment	Refers to IMP

Term	Definition
Subject eligible for continuing treatment in Study Period 3	At the Week 53 Visit, subjects may continue to the Study Period 3 if eligible. The basis for eligibility is a TIS ≥ 20 points at the Week 49 Visit. Subjects who continue the study will receive open-label IgPro20 0.5 g/kg SC infusions weekly in Study Period 3.

Abbreviations: See List of Abbreviations

1 Introduction

1.1 Background

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of acquired muscle disorders characterized by muscle weakness, elevated creatine kinase (CK) levels, myopathic electromyographic findings, characteristic histopathological findings [Malik et al, 2016; Anh-Tu Hoa and Hudson, 2017; Mandel et al, 2017; Milone, 2017; Schmidt, 2018], and in certain cases, an association with autoantibodies [Tieu et al, 2016; Schmidt, 2018]. IIM are best classified into 4 main subtypes: dermatomyositis (DM), polymyositis (PM), necrotizing myopathy, and inclusion body myositis [Malik et al, 2016; Milone, 2017]. The identification of the correct subtype and the distinction of these diseases from other disorders which have characteristics that mimic them is fundamental to treatment, because each subtype has a different prognosis and response to therapies [Dalakas, 2015].

Incidence and prevalence of DM varies greatly across studies. In a nationwide patient register and rheumatology quality register, the average incidence was 11 per 1,000,000 (13 for women and 9.7 for men) while prevalence rate was 14 per 100,000 (17 for women and 11 for men). Both incidence and prevalence rates increased with age with a peak in the 70 to 79 year range [Svensson et al, 2017].

Diagnosis of DM is achieved by the evaluation of a combination of clinical and pathological features. Dermatomyositis, with its characteristic skin rash and relatively greater responsiveness to corticosteroids and other immunomodulators than the other IIM subgroups, is quite distinguishable [Findlay et al, 2015; Oldroyd et al, 2017; Lahouti, 2015] and carries significant morbidity and mortality [Mandel et al, 2017]. If left untreated, muscle weakness leads to ambulation difficulties (restriction to wheelchair or confinement to bed). Within the patients with DM, a subgroup of patients with amyopathic/hypomyopathic DM has been identified. These patients present with characteristic rash but without obvious muscle weakness [Dalakas and Hohlfeld, 2003] or elevations in muscle enzyme [Ghazi et al, 2013]. This DM subgroup represents about 20% of all DM cases [Patel et al, 2018]. These patients are at increased risk of breast, lung, and ovarian cancer and may also have systemic involvement such as interstitial lung disease and cardiac disease [Udkoff and Cohen, 2016].

Primary treatment modalities include corticosteroids, intravenous immunoglobulin G (IVIG), plasmapheresis, and other immunomodulators (such as methotrexate, azathioprine, and cyclosporine A). In clinical practice, corticosteroids are usually the first choice medication in DM; however, long-term treatment with corticosteroids has significant side effects and is not well tolerated in patients [Yasir and Sonthalia, 2019]. One study estimated the 10-year

survival rate of 160 DM/PM patients treated with immunomodulators such as corticosteroids, methotrexate, and azathioprine to be 62% [Schiopu et al, 2012; Findlay et al, 2015], highlighting the continued unmet need in this disease.

The trigger that initiates DM or other IIM subtypes or causes flares is not clearly understood. However, it is known that environmental factors in genetically susceptible individuals can trigger myositis with involvement of several cellular and humoral mechanisms [Carstens and Schmidt, 2014]. In DM, inflammatory cells (predominantly $CD4^+$ cells) and perifascicular atrophy, in addition to immune attacks targeting capillaries leading to capillary loss and subsequent ischemia are observed. More recently, the importance of B lymphocytes, macrophages, and dendritic cells [Blank et al, 2014] and $CD4^+$ $CD25^+$ T-regulatory cells [Kessel et al, 2007] have been described as having a different role and weight in DM versus PM (where inflammatory cells [predominantly $CD8^+$ cells] are noted in the perimysium and in perivascular areas).

Because of the heterogeneity of IIM as mentioned above, and the possibility of different clinical outcomes among subtypes, this study will enroll only subjects with DM, including (clinically) amyopathic DM and adults first diagnosed with DM as juveniles (< 18 years old), to evaluate the safety and efficacy of IgPro20.

1.2 Information on IgPro20

1.2.1 Overview

IgPro20 is a ready-to-use 20% liquid formulation of human immunoglobulin G (IgG) with greater than 98% IgG purity for subcutaneous (SC) administration, and is manufactured by CSL Behring (CSLB). IgPro20 is approved in the United States of America, the European Union, Japan, and other countries under the brand name Hizentra® for SC administration in primary immune deficiency syndromes, chronic inflammatory demyelinating polyneuropathy (CIDP), and other indications.

The precise mechanism of action underlying immunoglobulin immunomodulatory treatment in autoimmune/immune-mediated and inflammatory disease is not fully understood. However, several mutually nonexclusive mechanisms have been proposed to explain the broad spectrum of action of immunoglobulin. These include anti-idiotype regulation, modifications in cytokine production, the inhibition of complement activation, the neutralization of autoantibodies, killing of target cells by antibody-dependent cytotoxicity, and the blockade of cell-cell interaction [Danieli et al, 2014].

A detailed description of the chemistry, pharmacology, efficacy, and safety of IgPro20 is provided in the IgPro20 Investigator's Brochure (IB).

1.2.2 Nonclinical Evaluation

Based on the overall assessment of the available nonclinical information from the different studies performed with IgPro20 or its stabilizers L-proline and polysorbate 80, there are no safety concerns with the administration of IgPro20. A detailed description of nonclinical studies of IgPro20 is provided in the IgPro20 IB.

1.2.3 Clinical Experience

To date, SC infusions of IgPro20 have been administered to humans in clinical studies in both immunodeficiency and immunomodulatory indications. This will be the first study in subjects with DM.

A detailed description of clinical studies of IgPro20 is provided in the IgPro20 IB.

1.3 Study Overview

This is a phase 3, multicenter, randomized, placebo-controlled, double-blind study of IgPro20 (subcutaneous immunoglobulin G [SCIG]) treatment in adult subjects with DM with or without muscle weakness. This study consists of a Screening Period (≤ 2 months), Study Period 1 (24 weeks of either IgPro20 or placebo administration), Study Period 2 (28 weeks of IgPro20 administration), and Study Period 3 (open-label IgPro20 administration until the end of the study) for subjects who have shown a treatment benefit at the End of Study Period 2 (EOP2). Study Period 3 will provide additional long-term safety and efficacy data for this patient population.

Subjects will be randomized to 1 of 2 treatment sequences:

- **Sequence A**: 0.5 g/kg IgPro20 for 24 weeks (Study Period 1) followed by 0.5 g/kg IgPro20 for 28 weeks (Study Period 2)

  - OR -

- **Sequence B**: placebo for 24 weeks (Study Period 1) followed by 0.5 g/kg IgPro20 for 28 weeks (Study Period 2)

After completing Study Period 2, eligible subjects may continue treatment with SC infusions of open-label IgPro20 0.5 g/kg in Study Period 3.

The primary objective of this study is to assess the efficacy of IgPro20 0.5 g/kg weekly SC doses in comparison to placebo in adult subjects with DM, as measured by responder status based on Total Improvement Score (TIS) assessments at Weeks 17, 21, and 25.

1.4 Potential Risks and Benefits

Identified and potential risks pertaining to IgPro20

Although the safety profile of IgPro20 has not been evaluated in subjects with DM, IgPro20 has been demonstrated in general to be a safe product based on safety data obtained from previous CSLB-sponsored clinical studies in various indications including primary immune deficiency and CIDP, and post-marketing experience collected over the past 9 years.

IgPro20 safety data has been accumulated in weekly doses up to 0.4 g/kg body weight. In a recently completed global CIDP program (one 24-week pivotal study IgPro20_3003 [172 subjects] and one 48-week extension study IgPro20_3004 [82 subjects]), 0.4 and 0.2 g/kg weekly doses were evaluated. In both CIDP studies, the systemic adverse event (AE) rate was low and local reactions were mild to moderate and decreased in frequency over time. For these reasons, no increased risk with 0.5 g/kg weekly is expected in this study.

Thrombotic and thromboembolic event (TEE) is an identified risk in class labeling for IVIG and SCIG. TEE is also an identified risk in the DM population [Nowak et al, 2016]. Any TEE in this study will be classified as an adverse event of special interest (AESI) (see Section 9.1.3 for details). Study stopping rules based on the observation of a prespecified increase in IgPro20 TEEs over placebo will be employed for this identified risk (see Section 3.9 for details).

Further details on identified and potential risks associated with IgPro20 are provided in the IgPro20 IB.

Potential risks pertaining to placebo

In this study, a 2% human albumin formulation will be used as placebo. The formulation will be developed by dilution of the commercially available liquid albumin preparation manufactured by the sponsor under Good Manufacturing Practice (GMP) conditions. The tolerability of SC administration of human albumin was tested in a pivotal CIDP study that included 57 subjects on placebo, and was found to be similar to that experienced with other plasma proteins, eg, IgG, as described above. No harm is to be expected from the use of albumin as placebo in DM subjects. The potential risk of disease flare in the placebo arm

during double-blind treatment has been mitigated by the provision of oral corticosteroid rescue treatment while continuing double-blind treatment until Week 25.

There is a high permeability for albumin between the SC compartment and the vascular system. In view of the SC data available, the absence of immunogenicity after intramuscular (IM) administration, and the high abundance of albumin in the body (> 25 mg/mL) [Poulsen, 1974], local reactions and immunogenicity are considered highly improbable at the dose administered in the present study.

Potential risks of failure of IgPro20

The efficacy of IgPro20 in DM is unknown. The potential risk of disease flare is mitigated by the provision of oral corticosteroid rescue treatment while continuing double-blind treatment until Week 25.

Potential benefit of IgPro20

A potential benefit of the study is the improvement of the symptoms of DM (eg, muscle strength, rash) as assessed by the outcome measures. Improvement in muscle strength and other measures has been noted in small preliminary studies using SCIG, based on literature [Cherin et al, 2016].

In addition, a low rate of systemic AEs as compared to those commonly seen with IVIG, and an increase in subject autonomy and quality of life through self-treatment may be observed.

IgG preparations in general have a well-known safety and efficacy profile documented in the literature [Eibl, 2003; Wittstock et al, 2003; Wittstock and Zettl, 2006] and as recently described in a completed CIDP study [van Schaik et al, 2018].

Thus, the associated benefit-risk is acceptable for DM subjects enrolled in the present study.

2 Study Objectives and Endpoints

2.1 Primary Objective and Endpoint

2.1.1 Primary Objective

The primary objective of this study is to assess the efficacy of IgPro20 0.5 g/kg weekly SC doses in comparison to placebo in adult subjects with DM, as measured by responder status based on the TIS assessments at Weeks 17, 21, and 25.

2.1.2 Primary Endpoint

Endpoint	Summary Measure
Responder status based on the TIS assessments at Weeks 17, 21, and 25	• Point estimate and 95% confidence interval (CI) for the responder rate by treatment sequence • Point estimate and 95% CI for the odds ratio (IgPro20:placebo)

A responder is defined as a subject with a TIS ≥ 20 points [Aggarwal et al, 2017] at Week 25 and at least 1 of the previous scheduled visits (Week 17 or Week 21), who completes 24 weeks of randomized IMP treatment (Study Period 1) without the use of rescue corticosteroid treatment. Note: for subjects who discontinue from IMP or the study for reasons which are related to the Ukraine war before Week 25, a multiple imputation approach will be used for dealing with missing TIS values (see Section 10.4.2.3).

2.2 Secondary Objectives and Endpoints

2.2.1 Secondary Objectives

The secondary objectives of the study are:

1. To assess the efficacy, with additional clinical outcome measures, of IgPro20 in comparison to placebo
2. To assess the safety of IgPro20 in comparison to placebo
3. To assess the safety and efficacy of IgPro20 at Week 53
4. To assess the safety of IgPro20 from after completion of Week 53 to the end of study participation

2.2.2 Key Secondary Efficacy Endpoints

Secondary Objective	Endpoint	Summary Measures
1	TIS at Week 25	• Mean TIS values at Week 25 by treatment sequence • Point estimates and 95% CI for mean difference (IgPro20 – placebo) at Week 25

Secondary Objective	Endpoint	Summary Measures
1	Change from Baseline in MMT-8 (Manual Muscle Testing of 8 muscle groups) at Week 25	• Mean changes from Baseline in MMT-8 at Week 25 by treatment sequence • Point estimates and 95% CI for mean change difference (IgPro20 – placebo) at Week 25
1	Change from Baseline in Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) total activity score at Week 25	• Mean changes from Baseline in CDASI total activity score at Week 25 by treatment sequence • Point estimates and 95% CI for mean change difference (IgPro20 – placebo) at Week 25
1	Reduction of oral corticosteroid dose at Week 25	• Number and percentage and 95% CI of subjects who are able to reduce the oral corticosteroid dose by ≥ 25% at Week 25 by treatment sequence • Point estimates and 95% CI for the odds ratio (IgPro20:placebo) at Week 25

2.2.3 Secondary Efficacy Endpoints

Secondary Objectives	Endpoints	Summary Measures
1, 3	TIS from Week 5 to Week 53	• Mean TIS by treatment sequence at each visit • Percentage of subjects achieving TIS ≥ 20, ≥ 40, and ≥ 60 points by treatment sequence at each visit • Time to first achieving TIS ≥ 20, ≥ 40, and ≥ 60 points by treatment sequence • Percentage of subjects achieving TIS ≥ 20 points at the end of the Study Period 2

Secondary Objectives	Endpoints	Summary Measures
1, 3	Individual core set measures (CSMs; except muscle enzyme) and CDASI from Baseline to Week 53	• Mean changes from Baseline by treatment sequence between Week 5 and Week 25 • Mean changes from Week 25 by treatment sequence between Week 29 and Week 53 Individual CSMs include: • Physician Global Disease Activity • Patient Global Activity Assessment • MMT-8 • Health Assessment Questionnaire – Disability Index • Extramuscular Global Assessment
1, 3	Definition of Worsening (DOW) from Baseline to Week 53	• Number and percentage of subjects meeting DOW at least once, twice, or > twice by treatment sequence • Time to meeting DOW for the first time by treatment sequence • Number and percentage of subjects meeting DOW and receiving rescue corticosteroid treatment by treatment sequence
1	Reduction of oral concomitant corticosteroid dose from Baseline to Week 53	• Number and percentage of subjects who start oral concomitant corticosteroid dose taper before Week 25 by treatment sequence • Number and percentage of subjects who are able to reduce their oral concomitant corticosteroid dose by ≥ 25%, ≥ 50%, and ≥ 75% by Week 25 or by Week 53 by treatment sequence
3	Use of rescue corticosteroid treatment from Baseline to Week 25	• Percentage of subjects receiving rescue corticosteroid treatment by treatment sequence and visit • Percentage of subjects whose rescue corticosteroid treatment is tapered by treatment sequence and visit • Time to first administration of rescue corticosteroid treatment
1, 3	Mobility, Self-care, and Usual Activities domains of EuroQoL 5-Dimension	• Number and percentage of subjects having at least 1 level, 2 levels, and > 2 levels of improvement from Baseline by treatment sequence at Week 13 and Week 25

Secondary Objectives	Endpoints	Summary Measures
	Questionnaire (EQ-5D-5L) to Week 53	• Number and percentage of subjects having no reduction in levels, at least 1 level, 2 levels, and > 2 levels of improvement from Week 25 by treatment sequence at Week 41 and Week 53

2.2.4 Safety Endpoints

Secondary Objective	Endpoint	Summary Measures
2,3,4	Treatment-emergent adverse events (TEAEs)	• Percentage of subjects with TEAEs • Percentage of subjects with related TEAEs • Percentage of subjects with serious TEAEs • Rate of TEAEs per time at risk • Rate of mild, moderate, and severe TEAEs per time at risk • Rate of related TEAEs per time at risk • Rate of serious TEAEs per time at risk

In addition to TEAEs for IMP and rescue corticosteroid treatment, safety will be assessed throughout the study based on laboratory assessment, physical examination, and vital signs. Specific monitoring for corticosteroid treatment, TEEs (including assessment whether study stopping rules were met [Section 3.9]), and hemolysis will also be performed (Sections 8.1.2.1, 8.1.2.2, and 8.1.2.3, respectively).

2.3 Exploratory Objectives and Endpoints

2.3.1 Exploratory Objectives

The exploratory objectives of this study are:

- **Study Period 1 and Study Period 2 (From Baseline to Week 53):**
  - To assess pain / discomfort and anxiety / depression domains of EQ-5D-5L
  - To assess Work Productivity and Activity Impairment Questionnaire for General Health (WPAI-GH)
  - To assess Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9)

- To assess Timed Up and Go result for functional ability to rise from a chair and ambulate
- To assess itch (pruritus)
- To assess muscle enzymes
- To assess antinuclear antibody (ANA), myositis-specific autoantibodies (MSA), and myositis-associated autoantibodies (MAA)
- To assess the pharmacokinetics (PK) of IgG in Week 37

- **Study Period 3 (after Week 53):**
  - To assess the efficacy of IgPro20 from after completion of Week 53 to the end of study participation
  - To assess quality of life of IgPro20 from after completion of Week 53 to the end of study participation
  - Use of corticosteroid treatment from Week 53 to the end of study participation

3 Study Design and Oversight

3.1 Overall Design

This is a phase 3, multicenter, randomized, placebo-controlled, double-blind study of IgPro20 (SCIG) treatment in adult subjects with DM, with or without muscle weakness.

This study consists of Screening and 3 treatment periods:

- Screening Period: Up to 2 months during which screening assessments must be completed.
- Study Period 1: 24 weeks of either IgPro20 or placebo administration.
- Study Period 2: 28 weeks of IgPro20 administration.
- Study Period 3: additional treatment with open-label IgPro20 for subjects who have shown treatment benefit (see Section 4.1.3 for details) at Week 53. See Section 3.7 for the definition of end of study.

After Screening, subjects will be randomly assigned (1:1) to 1 of 2 sequences of double-blind weekly IMP treatment (0.5 g/kg IgPro20 and placebo). Subjects assigned to **Sequence A** will receive 0.5 g/kg IgPro20 for 24 weeks (Study Period 1) followed by 0.5 g/kg IgPro20 for 28 weeks (Study Period 2). Subjects assigned to **Sequence B** will receive placebo for 24 weeks (Study Period 1) followed by 0.5 g/kg IgPro20 for 28 weeks (Study Period 2).

The study data will be unblinded for the primary data analysis (ie, EOP1 analysis) after all subjects have completed all assessments for Study Period 1 and the data has been cleaned for primary data analysis. Subjects and caregivers, as well as site personnel involved in the conduct of the study, will remain blinded to treatment allocation until all subjects have completed all assessments for Study Period 2.

At the Week 53 Visit, subjects may be eligible to continue to Study Period 3 if their TIS was ≥ 20 points at the Week 49 Visit. In Study Period 3 subjects will receive open-label IgPro20 0.5 g/kg SC infusions weekly until the end of the study (Section 3.7).

The study population consists of subjects with the diagnosis of IIM according to European League Against Rheumatism/American College of Rheumatology (EULAR / ACR) criteria [Lundberg et al, 2017] and the presence of an active specific DM rash or other objective evidence. In addition, subjects must present with a defined degree of disease severity, manifested by a decrease in strength (MMT-8) or affected skin (CDASI) and a global physician impression (on a visual analog scale [VAS]).

At Baseline (Week 1, before infusion of IMP), the site physicians must confirm that no clinically relevant improvement has occurred since the Screening Visit. Clinically relevant improvement is defined as ≥ 2 cm improvement on a 10-cm Physician Global Disease Activity Assessment VAS. A sufficient number of subjects will be screened in order to randomize approximately 126 subjects into the study. Subjects will be randomized at a 1:1 ratio to receive either **Sequence A** or **Sequence B** during Study Period 1 and Study Period 2.

During the first 24 weeks of IMP treatment, subjects will receive either IgPro20 0.5 g/kg SC or placebo (Study Period 1); during the subsequent 28 weeks all subjects will receive IgPro20 at a dose of 0.5 g/kg (Study Period 2); and additionally, subjects will be treated with open-label IgPro20 0.5 g/kg SC on a weekly basis until the end of the study (Study Period 3).

If clinically relevant improvement is achieved at Week 17, the subject's concomitant oral corticosteroid dose (≤ 20 mg/day prednisolone equivalent at Baseline) must be tapered downward according to the guidance provided (Section 5.3.2) and physiotherapy regimen may be modified. Prior to Week 17, the dose of corticosteroids should remain stable unless intolerance or side effects require dose reduction.

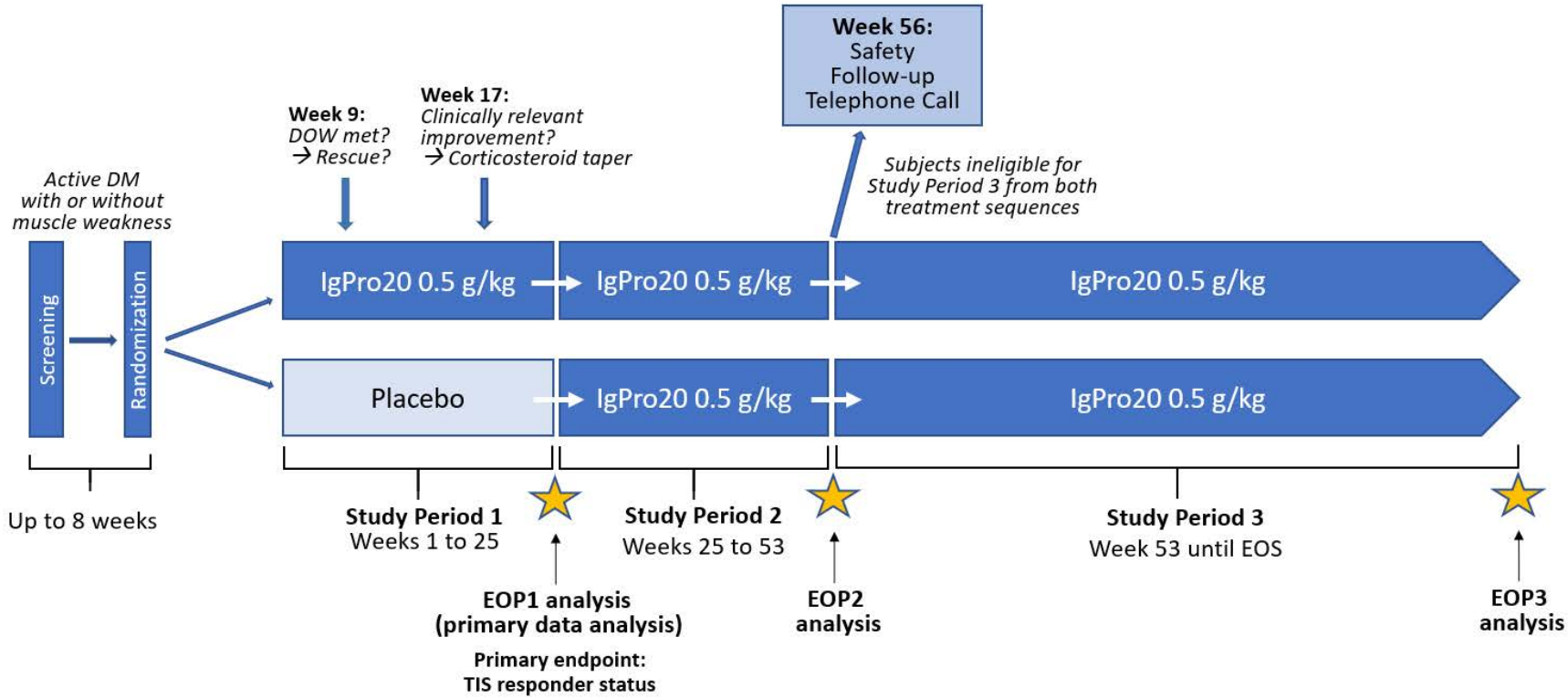
In the event of clinical worsening at or after Week 9, site physicians may provide rescue corticosteroid treatment to subjects. Clinical worsening in this study is defined by meeting the criteria for DOW. If an unscheduled visit is used for DOW assessment, the 2 assessments

must be done at study visits at least 2 weeks apart. The oral rescue corticosteroid (prednisolone equivalent) treatment should be provided as per the Treating Physician's standard of care (see Section 5.3.1). Any oral corticosteroid rescue treatment given during the first 24 weeks of randomized IMP treatment should be tapered by Week 25 as much as clinically possible to the corticosteroid dose at Baseline. Subjects who have received rescue corticosteroid treatment before Week 25 will be considered non-responders for the primary endpoint (see Section 2.1.2) and will continue study participation and IMP treatment. All subjects continuing in the study after Week 25 will receive IgPro20 treatment until Week 53.

At Week 53, eligibility for continuation of open-label IgPro20 treatment in Study Period 3 will be confirmed based on the TIS conducted in Week 49 (see Section 4.1.3 for details). If subjects do not continue treatment after Week 53, an EOP2 Safety Follow-up Telephone Call will be conducted to assess the subject's safety status at Week 56 (or 4 weeks after the final infusion). If the subject continues treatment in Study Period 3, the telephone call will not be performed.

See Section 3.7 for the definition of study end.

Figure 1 Study Design



Abbreviations: DM = dermatomyositis; DOW = Definition of Worsening; EOP = End of Study Period; TIS = Total Improvement Score.

3.2 Dose and Dosing Regimen

Subjects will be randomized 1:1 into 1 of 2 weekly treatment sequences:

Sequence A: 0.5 g/kg IgPro20 for 24 weeks (Study Period 1) followed by 0.5 g/kg IgPro20 for 28 weeks (Study Period 2)

OR

Sequence B: placebo for 24 weeks (Study Period 1) followed by 0.5 g/kg IgPro20 for 28 weeks (Study Period 2)

In Study Period 3, subjects who show benefit (TIS ≥ 20 points) at Week 49 will receive open-label 0.5 g/kg IgPro20 until the end of the study (Section 3.7).

3.3 Scientific Rationale

3.3.1 Study Design Rationale

In this study, the EULAR/ACR classification criteria will be used to confirm the DM diagnosis. In short, the EULAR/ACR classification criteria assigns a numeric score to subjects with various clinical features such as skin and other clinical manifestations, muscle weakness patterns, laboratory evaluations, and muscle biopsy features. The aggregate score obtained will allow the subject to be classified with probable or definite IIM, and then presence of specific rash or other objective evidence (eg, muscle biopsy) will be used to identify the subjects with DM [Lundberg et al, 2017].

Evidence for the efficacy of immunoglobulin (IVIG or SCIG) treatment in patients with DM is limited. IVIG was shown to be efficacious in 2 randomized controlled studies of DM. The first study reported in 1993 by Dalakas et al, randomized 15 subjects with refractory disease to either corticosteroids and placebo or corticosteroids and high dose IVIG (1 gram/kg/day × 2 days monthly for 3 months). The authors reported that subjects treated with IVIG had a significant improvement in scores of muscle strength ($p < 0.018$) and neuromuscular symptoms ($p < 0.035$) compared to subjects treated with placebo who had no change. The second study reported in 2008 by Tian et al, randomized 60 elderly (> 60 years of age) subjects with DM to either corticosteroids or corticosteroids and low dose IVIG (0.4 gram/kg/day × 3 days monthly for 3 months). The authors reported greater clinical and biochemical improvements in the group treated with IVIG compared to those who were not treated with IVIG and minor side effects. In addition to these 2 existing randomized controlled studies of IVIG therapy in DM, several prospective and retrospective open-label

studies have been conducted and are summarized in a systematic review [Wang et al, 2012]. Clinical improvement was reported in up to 93% of subjects in early and therapy-refractory DM/PM; the typical dose was 2 g/kg IVIG given over 3 to 6 months. It has been reported that long-term use of IgG therapy is safe and effective, but this has not yet been confirmed in clinical studies. In a retrospective long-term study, 42 subjects with DM were followed; 24 received IVIG therapy regularly. After 6 months of treatment, most IVIG-treated subjects (91.7%) presented with muscular disease remission, compared to 55.6% of non-IVIG-treated subjects ($p = 0.007$). During long-term IVIG treatment (up to 48 months), 16.7% of subjects presented with muscular relapses, which is significantly less than those who received no or only a few IVIG courses. The overall relapse-free period from any DM symptom was 38.5 ± 24.3 months [Kampylafka, 2012].

SCIG has also been shown to be efficacious in treating subjects with DM/PM in smaller uncontrolled studies [Schleinitz et al, 2008; Danieli et al, 2011; Danieli et al, 2014; Gelardi et al, 2014; Cherin et al, 2016]. Long-term use of SCIG therapy has been described by Cherin [Cherin et al, 2016]. In doses of 1.9 g/kg monthly, 19 subjects were treated for a mean of 18.8 months. Median doses infused were 180 mL/week using 2 infusion pumps; similar to the infusion parameters in this study. Although these smaller studies have shown promising results, no large-scale or randomized controlled studies are available to corroborate the efficacy of SCIG against placebo in subjects with DM, which is a reason for the initiation of this study.

This study will build on previous evidence that has shown efficacy in the first 3 to 6 months of IgG treatment and will investigate whether the initial improvement can be sustained for 6 months to up to 7 years.

The primary endpoint of this study is based on the TIS [Aggarwal et al, 2017]. The TIS is a sum response criterion which incorporates 6 weighted International Myositis Assessment and Clinical Studies (IMACS) CSMs, previously validated for the assessment of DM and PM [Rider et al, 2003; Rider et al, 2002]. They include physician and patient global activity on a 10-cm VAS, muscle strength measured by manual muscle testing (MMT-8), physical function measured by the Health Assessment Questionnaire, extramuscular global activity measured by the physician on a 10-cm VAS, and the most abnormal serum muscle enzyme. The TIS was evaluated on patient profiles using expert consensus (gold standard) and was validated using data from a clinical study [Oddis et al, 2013], the largest study done in DM and PM so far. A total improvement score (range: 0 to 100), determined by summing scores for each CSM, was based on improvement in and relative weight of each CSM. Thresholds for minimal, moderate, and major improvement were ≥ 20, ≥ 40, and ≥ 60 points on the TIS.

The TIS was chosen as the basis for the primary endpoint of this study given the fact that no single CSM adequately covers all the domains in DM. For example, muscle enzyme levels can be normal in active DM, and active muscle weakness in DM can occur without active rash. The previously developed IMACS response criteria were based on at least 20% improvement in 3 of 6 CSMs, with no more than 2 CSMs worsening by at least 25% (which cannot be muscle strength). The limitations of these criteria included that equal weights had been applied to each CSM and a quantitative or continuous outcome was lacking.

Given that the TIS is focused on improvement, one of the limitations is that it cannot differentiate between no change and worsening and, therefore, these criteria might not be applicable in studies of worsening disease activity (ie, disease flare designs) in DM. However, this study will only include subjects with active disease with background immunomodulatory therapy and IgPro20 will be used as add-on therapy. It is, therefore, not expected that a relevant number of subjects will experience disease flares that meet the criteria for DOW. Any subject who meets DOW criterion will be offered standard-of-care rescue corticosteroid treatment until recovery. By definition of the primary endpoint, these rescued subjects will be classified as treatment failures (non-responders).

With the abovementioned limitations of TIS in identifying deterioration, key secondary endpoints have been defined that allow for identification of both improvement and deterioration and that are relevant in the assessment of DM. MMT-8 is a set of 8 designated muscles which will be tested bilaterally (potential score 0 to 150): 7 biaxial muscles with potential score 0 to 140 and 1 axial (neck flexors) with potential score 0 to 10. Validation of MMT-8 has demonstrated internal reliability and consistency, rater reliability, convergent construct validity, and responsiveness in assessing strength in patients with adult DM (also in PM and juvenile IIM) [Rider et al, 2010]. The MMT-8 is 1 of the CSMs and is the most heavily weighted CSM in the TIS.

The CDASI in its modified version (version 2) is a validated tool of skin disease activity (3 items) and damage (3 items) assessment. It has been developed as an instrument for clinical studies and longitudinal patient assessment [Klein et al, 2008; Goreshi et al, 2012; Yassaee et al, 2010].

These 2 validated tools (MMT-8 and CDASI) will enhance knowledge on the outcome data as key secondary endpoints, as these 2 domains (muscle strength and skin disease activity) are the most relevant manifestations of DM. They will provide evidence of treatment effect to supplement the composite improvement scale — TIS.

The primary endpoint will be assessed at Weeks 17, 21, and 25. In Study Period 2, all subjects will be on IgPro20 treatment; subjects who were previously allocated to placebo will have the opportunity to respond to IgPro20 treatment, and subjects who were already treated with IgPro20 in Study Period 1 will have the opportunity to maintain or improve their response. In addition, starting at Week 17, stable background concomitant corticosteroid treatment must be tapered, if the subject has demonstrated clinically relevant improvement, ie, ≥ 2 cm improvement from Baseline on a 10-cm Physician Global Disease Activity Assessment VAS (see Section 5.3.2). Tapering concomitant corticosteroid treatment will reduce the risk for steroid-related side effects, eg, uncontrolled hypertension, hyperglycemia, and weight gain.

Study Period 3 of the study will provide data on the long-term safety and efficacy of treatment with IgPro20. Eligible subjects may continue treatment with open-label IgPro20 in Study Period 3 starting at Week 53. The study will end CCI :

CCI months CCI

CCI

CCI for the indication Dermatomyositis, unless the decision has been made by CSLB that CCI) is not reasonably possible, in which case the study will end 6 months after notice is provided to the applicable regulatory authorities of that decision.

3.3.2 Dose Rationale

The few small studies that have utilized SCIG for treatment in patients with DM/PM relied on precedence from IVIG dosing to determine optimal SCIG dosing. From the first study in 1987 in a single subject with PM, to the Dalakas 1993 study and 2 Japanese studies, a 2 g/kg body weight per month IVIG dose was used as a standard dose in treatment of subjects with DM/PM [Dalakas, 1991; Dalakas et al, 1993; Saito et al, 2008; Miyasaka et al, 2012], and has been commonly adopted in clinical practice and standard of care. In smaller, open-label studies, similar SCIG monthly doses were used (2 g/kg body weight [Danieli et al, 2011; Gelardi et al, 2014], 1.9 g/kg body weight [Cherin et al, 2016], and 1.7 g/kg body weight [Schleinitz et al, 2008]) in subjects with DM/PM. In these studies, the standard IVIG dose for subjects with DM/PM was divided into weekly SCIG doses approximately equivalent to 0.5 g/kg body weight per week. Positive responses were noted as early as 3 months (the earliest tested time points for improvement). In addition, CSLB performed a simulation using a previously developed population PK model based on data from subjects with CIDP (mechanism of action postulated to be immunomodulatory) to assess in subjects with DM, predicted IgG exposure after treatment with a 0.5 g/kg SC dose of IgPro20. These analyses predicted that the median average concentration estimated as area under the concentration-time curve for a specific time interval ($AUC_{0\text{-time}}$)/dosing interval was comparable following 2 g/kg monthly IVIG (22.20 g/L) and 0.5 g/kg weekly SCIG (20.85 g/L), after 8 to 10 weeks. The analysis also predicted trough concentration (C_{trough}) at steady state, which appears to be higher for 0.5 g/kg weekly SCIG (17.12 g/L) compared to 2 g/kg monthly IVIG (13.15 g/L). The higher C_{trough} following 0.5 g/kg SCIG dose is likely due to a shorter dosing interval following weekly dosing. Overall, this analysis provides evidence of comparable steady-state IgG exposure after SC dosing of 0.5 g/kg body weight weekly and IV dosing of 2 g/kg body weight monthly. Based on the clinical evidence and outcome of the simulations, we have chosen 0.5 g/kg body weight as the weekly IgPro20 dose in this study.

A weekly flexible SC infusion dosing regimen will be employed during the study. This means that the subject and study site can select the most appropriate and convenient regimen based on body weight and subject preference (see Appendix 15 for examples). The maximum volume per infusion will be 50 mL which can be divided into up to 3 infusion sites per infusion. The infusion rate can be increased gradually to 50 mL/h per infusion site, as tolerated during the study.

This will be the first clinical study performed with IgPro20 for the treatment of DM.

3.4 Planned Study Duration

After up to 2 months of Screening, the duration for an individual subject is expected to be 24 weeks in Study Period 1 and 28 weeks in Study Period 2. The maximum study duration in the open-label Study Period 3 will be approximately 7 years; however, subject participation will end if the drug becomes commercially available or if there is no longer benefit from the study drug. For subjects not eligible to participate in Study Period 3, study duration will be up to 56 weeks (including the Follow-up Telephone Call).

See Section 3.7 for the definition of end of study.

3.5 Planned Number of Subjects

A sufficient number of subjects will be screened in order to randomize approximately 126 subjects into the study (63 per treatment sequence) at approximately 80 to 100 study sites globally. At least 10 Japanese subjects will be randomized at study sites in Japan.

3.6 Definition of Start of the Clinical Study

The start of the clinical study is defined as the date of the first signed informed consent of a potential subject.

3.7 Definition of End of the Clinical Study

The study will end CCI :

CCI months CCI

CCI

CCI for the indication Dermatomyositis, unless the decision has been made by CSLB that CCI is not reasonably possible, in which case the study will end 6 months after notice is provided to the applicable regulatory authorities of that decision.

3.8 Study Oversight

3.8.1 Steering Committee

The steering committee will provide scientific support, scientific expertise for substantial amendments to the protocol, advice to the investigators on all aspects of the study, and support recruitment/feasibility of the study (ie, educational training or lectures) and preparation of publications. The steering committee will consist of external experts in the

fields of dermatology, rheumatology, neurology, and statistics who have experience treating patients with DM and/or experience in clinical studies.

3.8.2 Independent Data Monitoring Committee

The independent data monitoring committee (IDMC) will monitor the efficacy and safety data generated during Study Period 1 and Study Period 2 (through Week 53 / Week 56) in order to conduct assessments of the benefit-risk profile. The IDMC will consist of external experts in the fields of dermatology, rheumatology, neurology, hematology/coagulation, and statistics who have experience treating patients with DM and/or experience in clinical studies. The IDMC will receive notification of all serious adverse events (SAEs), AESIs, and deaths reported throughout the study. In addition, the IDMC will meet at regularly scheduled intervals to evaluate compiled efficacy and safety data to assess overall benefit-risk. After each meeting, recommendations will be issued to CSLB regarding the continuation of the study, potential need for protocol modifications, or study termination. No success or futility thresholds will be set for the IDMC reviews; CSLB will not stop the study based on these data unless a major safety issue has been identified (see Section 3.9). The composition, activities, and responsibilities of the IDMC will be described in the IDMC Charter.

3.9 Thromboembolic Event Stopping Criteria

The elevated risk of TEEs associated with IgPro20 treatment as compared with placebo will be evaluated by the IDMC on an ongoing basis and at the defined data cut points described below.

Data Cut Point – percentage of subjects having reached the end of the primary endpoint analysis period (Week 25):

- 25%
- 50%
- 75%
- 100%

TEE rates will be calculated for each treatment group, along with relative risk (IgPro20 over placebo) and associated 80% credibility intervals based on Bayesian technique [Barker et al, 2008] which accounts for the consideration of differential exposure times. The analysis will include data from Study Period 1 and Study Period 2, as available. Further details and calculations will be provided in the IDMC statistical analysis plan.

An excess of TEEs in IgPro20 over placebo will be considered if the lower limit of the 80% credibility interval for the relative risk is > 1.1 (presumably an IgPro20 rate greater than 10% [relative] over placebo). In this case the IDMC may recommend stopping the study.

Further details on how the IDMC will review the TEE data and provide recommendations is included in the IDMC Charter.

Monitoring of TEE risk is described in Section 8.1.2.2.

4 Selection and Withdrawal of Subjects

4.1 Eligibility Criteria

The study population will be selected on the basis of the inclusion and exclusion criteria described in the sections below. Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Subject eligibility should be reviewed and documented by an appropriately medically qualified member of the investigator's study team before subjects are included in the study. Full eligibility for the study will be determined at Baseline.

4.1.1 Inclusion Criteria

To be enrolled and randomized into the study, subjects must meet all of the following inclusion criteria:

1 Capable of providing written informed consent by signing an informed consent form (ICF) and willing and able to adhere to all protocol requirements

2 Age ≥ 18 years

3 **Diagnosis** of at least probable IIM per EULAR/ACR Classification Criteria (Appendix 2): minimum aggregate score of 5.5 without muscle biopsy and 6.7 with muscle biopsy (historical muscle biopsy is acceptable) which includes confirmation of DM rash/skin manifestation (present or by history [historical skin biopsy is required for amyopathic DM subjects])

4 **Disease activity** defined by:

- Presence of DM rash/skin manifestation (eg, Gottron's papules/sign, heliotrope rash, periorbital edema, V sign, Shawl sign) at Screening Visit - OR -

- One objective disease activity measure within 3 months before Baseline:
  a. Magnetic resonance imaging (MRI) scan showing active inflammation (edema) of a proximal skeletal muscle - OR -
  b. Electromyogram showing acute changes such as spontaneous activity not explained by other disease - OR -
  c. Muscle biopsy with perivascular or perimysial inflammation - OR -
  d. CK > 4 times the upper limit of normal (4 × ULN)

5 **Disease severity** at Screening and Baseline defined by a minimum value of 2 cm on a 10-cm Physician Global Disease Activity VAS* and:

- MMT-8 ≤ 142 – OR -
- CDASI total activity score ≥ 14

* On the VAS, 0 cm = absence of disease activity and 10 cm = extremely active/severe disease activity.

6 Subject has failed previous DM treatment or is on DM treatment such as immunosuppressants and/or antimalarials on a stable dose ≥ 3 months before Baseline; and/or oral corticosteroids (≤ 20 mg/day prednisolone equivalent) on a stable dose ≥ 1 month before Baseline (also see Section 7.2 for details)

4.1.2 Exclusion Criteria

Subjects must not be enrolled or into the study or randomly assigned to treatment if they meet any of the following exclusion criteria:

1 Cancer-associated myositis, defined as the diagnosis of myositis within 2 years of the diagnosis of cancer

2 Evidence of malignancies diagnosed within the previous 5 years

Note: *Subjects with a history of carcinoma in situ of the cervix that has been excised and cured with ≥ 5 years since excision or subjects with documented history of treated basal or squamous cell skin cancer may be enrolled into the study.*

3 Physician Global Damage Assessment ≥ 3 on a 5-point Likert scale where a score of 3 represents severe damage

4 Clinically relevant improvement between Screening and Baseline, defined by ≥ 2 cm improvement on a 10-cm Physician Global Disease Activity Assessment VAS

5 Known or suspected hypersensitivity or other severe reactions to IgPro20 or to any of its excipients, or other immunoglobulins or severe reactions to blood products

6 Other significant medical conditions that could increase the risk to the subject, eg:

- History of allogeneic bone marrow/stem cell transplant/solid organ transplant
- Cardiac insufficiency (New York Heart Association Class III or IV) or unstable ischemic heart disease
- Chronic kidney disease stage IV or V
- Recent surgery requiring general anesthesia within the previous 4 weeks before Screening
- Known hyperprolinemia type I or type II
- Thrombophilic abnormalities including blood hyperviscosity, protein C or protein S deficiency, antithrombin-III deficiency, plasminogen deficiency, antiphospholipid antibodies, Factor V Leiden mutation, dysfibrinogenemia, or prothrombin G20210A mutation
- History of documented thrombotic episode, eg, pulmonary embolism (PE), deep vein thrombosis (DVT), myocardial infarction, thromboembolic stroke at any time
- More than 3 of the following specified risk factors for TEEs (documented and current conditions) occurring concurrently: atrial fibrillation, coronary disease, diabetes mellitus, dyslipidemia, hypertension, obesity (body mass index ≥ 30 kg/m^2), recent significant trauma and immobility (wheelchair-bound or bedridden)
- Uncontrolled, severe, or rapidly progressive interstitial lung disease which will prevent the subject from successful participation in the study
- Severe skin disease at planned infusion sites that would make SC infusions infeasible
- Medical conditions whose symptoms and effects could alter protein catabolism and or IgG utilization (eg, protein-losing enteropathies, nephrotic syndrome, known immunoglobulin A [IgA] deficiency with antibodies to IgA)

7 Other conditions which would prevent correct assessment or lead to impaired muscle strength (eg, other neurological disorders including, but not limited to, Parkinson's disease or severe musculoskeletal conditions like severe osteoarthritis or deformities)

8 Laboratory exclusions at screening:

- Positive result at for any of the following: human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV)
- Creatinine > 1.5 × ULN or blood urea nitrogen (BUN) > 3 × ULN

9 Any of the following therapies:

- Within **1 month** before Baseline: IM, IV, or intra-articular corticosteroids including adrenocorticotropic hormone (any dose), doses > 20 mg/day prednisolone equivalent (any route), or any change to physiotherapy
- Within **2 months** before Baseline: IgG (Note: Subject may enroll < 2 months after stopping IgG therapy if clinical deterioration is experienced after withdrawal.)
- Within **3 months** before Baseline: plasma exchange or plasmapheresis
- Within **6 months** before Baseline: cyclophosphamide or alkylating agents
- Within **6 months or 5 half-lives** of the drug, whichever is longer, before Baseline: other biologic therapies including investigational agents
- Within **9 months** before Baseline: rituximab or evidence of persistent B cell depletion after stopping therapy

10 Male subject or female subject of childbearing potential either not using or not willing to use a medically reliable method of contraception (see Section 7.4.2), not sexually abstinent during the study, or not surgically sterile before study enrollment

11 Pregnant or breastfeeding

12 Alcohol, drug, or medication abuse within 1 year of providing informed consent

13 Previously received IMP in this study or failed Screening more than 1 time in this study

14 Involved in the planning and/or conduct of this study (applies to CSLB staff, staff at the study site, and third-party vendors)

15 Any issue that, in the opinion of the investigator, would render the subject unsuitable for participation in the study or unable to comply with study procedures, eg, inability to self-administer IMP or by aid through a caregiver

4.1.3 Eligibility Criteria for Study Period 3

At the Week 53 Visit, subjects may continue to Study Period 3 if they have a TIS ≥ 20 points at the Week 49 Visit. Subjects who participate in Study Period 3 will continue to receive open-label IgPro20 0.5 g/kg SC infusions weekly until the end of the study (Section 3.7).

4.2 Screen Failures

Screen failures are defined as individuals who consent to participate in the clinical study but who do not meet the eligibility criteria for participation (see Section 4.1) by Baseline.
A minimal set of information including demography, eligibility criteria, screen failure details, and any SAE should be recorded for all individuals considered screen failures.

Individuals who do not meet the eligibility criteria by Baseline (ie, screen failure) other than actual DM diagnosis and disease activity may be rescreened once for failed eligibility.

4.3 Discontinuation of IMP and Subject Study Withdrawal

4.3.1 Discontinuation of IMP

If any of the following apply, the subject must discontinue IMP:

- Subject wishes to discontinue IMP
- Subject withdraws consent for study participation
- Investigator advises that the subject's safety or well-being could be compromised by further treatment
- Subject or caregiver is not able to administer the SC infusions at home by Week 4
- Subject has confirmed diagnosis of DVT or PE
- Subject has Grade 3 hemolysis (see Section 8.1.2.3)
- Subject becomes pregnant
- Relevant treatment noncompliance

During participation in Study Period 3, if the investigator determines that the subject is no longer benefiting from IgPro20 and/or is showing signs of clinical deterioration in DM status, the subject must be discontinued from the study.

The investigator should record in the electronic case report form (eCRF) and in the subject's medical records the reason and date of IMP discontinuation.

Subjects who discontinue IMP will be encouraged to remain in the study until Week 25 if discontinuation occurs during Study Period 1, or until Week 53 if discontinuation occurs during Study Period 2, in order to collect study assessments. The Safety Follow-up Telephone Call will not be performed for subjects who discontinue IMP treatment but remain in the study for at least 1 subsequent study visit 4 weeks after IMP discontinuation. See Schedule of Assessments for details on assessments no longer collected after IMP discontinuation if the subject remains in the study, and Section 4.3.2 for details on handling subject withdrawal from study.

Subjects who discontinue IMP during Study Period 3 will be withdrawn from the study. Withdrawal from IMP Study Period 1 or Study Period 2 renders a subject ineligible for participation in Study Period 3 of this study.

4.3.2 Subject Withdrawal from Study

Subjects may withdraw from the study at any time at their own request or at the discretion of the investigator or CSLB. The investigator should record in the eCRF and in the subject's medical records the reason for study withdrawal, if provided by the subject in the case of withdrawn consent, and date of subject withdrawal.

In accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) principles of Good Clinical Practice (GCP), the investigator always has the option to advise a subject to withdraw from treatment or the study if the subject’s safety or well-being is compromised by his or her further participation in the study. Concern for the interests of the subject must always prevail over the interests of the study.

4.3.2.1 Procedures for Handling Withdrawals

If a subject is withdrawn from the study during Study Period 1 or Study Period 2, attempts will be made to complete and document the Week 53 assessments. If the subject is withdrawn from the study after receiving IMP, every effort will be made to ensure that the relevant safety assessments, including the 4-week Safety Follow-up Telephone Call (only in Study Period 1 and Study Period 2), are completed.

If the subject is withdrawn from the study during Study Period 3, the EOP3 Visit assessments must be performed. The subject may also be asked by the investigator to complete additional study assessments. If, during Study Period 3, the investigator determines that the subject is no longer benefiting from IgPro20 and/or is showing signs of clinical deterioration in the status of DM, the subject must be discontinued from the study. If the subject withdraws from the study, and also withdraws consent for disclosure of future information, CSLB may retain and continue to use any data and samples collected before withdrawal of consent.

4.3.3 Subjects Lost to Follow-up

If a subject repeatedly fails to return for scheduled visits, the site must attempt to contact the subject and counsel the subject on the importance of maintaining the assigned study visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study. All attempts to contact the subject should be documented in the subject's medical record.

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

4.3.4 Replacement Policy

Subjects withdrawn from the study will not be replaced.

4.3.5 Consequences of Subject Withdrawal or IMP Discontinuation

Subjects who have been withdrawn from the study or who have discontinued IMP before Week 25 will be considered non-responders for the primary endpoint analysis, except if withdrawal or discontinuation was due to the Ukraine war (see Section 10.4.2) Withdrawal from IMP during Study Period 1 or Study Period 2 renders a subject ineligible for participation in Study Period 3 of this study.

5 Study Interventions

5.1 Investigational Products

5.1.1 Description of IgPro20

Substance name	IgPro20
Active substance	Human normal IgG
Trade name	Hizentra®
Storage	Temperature-controlled and monitored conditions at 2 to 8°C in a secure storage area at the site
Dosage form	Liquid, ready-to-use 20% IgG solution stabilized with 250 mmol/L L-proline and 20 mg/L polysorbate 80

IgG = immunoglobulin G.

IgPro20 for SC administration will be provided as a 20% IgG solution in a vial containing 10 g IgG in a 50 mL volume. IgPro20 will be manufactured by CSLB, in accordance with ICH GMP guidelines and local regulatory requirements.

Information on the preparation and SC administration of IgPro20 is provided in the IMP manual.

5.1.2 Description of Placebo

Substance number	Not applicable
Substance	Placebo
Trade name	Not applicable
Storage	Temperature-controlled and monitored conditions 2 to 8°C in a secure storage area at the site
Dosage form	2% human albumin solution in 250 mmol/L L-proline and 20 mg/L polysorbate 80 manufactured from the licensed, pasteurized CSLB human albumin 5% final product

CSLB = CSL Behring.

Placebo for SC administration will be manufactured by CSLB, and provided in vials of 50 mL volume.

5.1.3 Dosing and Administration of IgPro20 and Placebo

The investigator (or delegate) will dispense or administer IMP only to subjects included in this study following the procedures set out in this study protocol. Information on the dosing characteristics of IMP is provided in Table 5.

Table 5 Investigational Medicinal Product Dosing Characteristics

SC Infusion Parameter	IgPro20	Placebo
Route	SC	SC
Anatomical location	Abdomen, thigh, upper arm, and/or lateral hip	Abdomen, thigh, upper arm, and/or lateral hip
Total infusion volume	Dependent on body weight (eg, 80 kg subject, 200 mL)	Dependent on body weight (eg, 80 kg subject, 200 mL)
Infusion duration	Volume and number of infusion sites dependent	Volume and number of infusion sites dependent

SC = subcutaneous.

All IMP in the study will be administered by SC infusions as weekly doses of 0.5 g/kg. At least the first SC infusion for Week 1 and Week 2 must be administered during the study visit at the investigational site to allow for training and confirmation of appropriate SC infusion technique. After Week 1 and Week 2, all weekly SC infusions will be self-administered at home. The SC infusions can be performed on 1, 2, 3, or 4 days each week and more than 1 infusion can be performed on a single day. It is preferred that the SC infusions be performed in a similar way throughout the study, ie, the same number of infusions and the same number of days each week after Week 2; however, the dosing regimen can be adjusted during the study in case of intolerability or inconvenience. All SC infusions for the previous week must be performed before the following study visit, eg, all Week 4 SC infusions performed before the day of the Week 5 Visit. Body weight will be measured at every study visit and changes in body weight > 2 kg will require a dose volume adjustment. The total dosing volume of IMP will be managed by the interactive response technology (IRT) system. Preparation instructions are provided in the IMP manual.

Subcutaneous Infusion Dosing Regimen Example:

Total dose volume per week needed for 80 kg subject = 200 mL. See Appendix 15 for weekly weight-based dosing regimen table.

Infusion dosing options may include but are not limited to the following:

- Total volume can be delivered on 1 day using 4 infusions of 50 mL
- Total volume can be delivered on 2 days using 2 infusions of 50 mL each day
- Total volume can be delivered on 3 days using 1 infusion of 50 mL each for 2 days and 2 infusions of 50 mL on the third day
- Total volume can be delivered on 4 days using 1 infusion of 50 mL each day

The SC infusions should be performed at appropriate infusion sites (eg, on the abdomen, thighs, upper arm, and/or lateral hip). The number of infusion sites is dependent upon the total volume administered. The maximum rate and the maximum volume per infusion site should not be exceeded and increases up to the maximum should be done gradually as tolerated.

Subcutaneous Infusion Volume and Rate of Infusion:

- **Volume (mL/Site):** ≤ 20 for Week 1 and ≤ 50 as tolerated for all subsequent study weeks
- **Rate of infusion (mL/hour/site)**: ≤ 20 for Week 1 and ≤ 50 as tolerated for all subsequent study weeks

Subcutaneous Treatment Training

Every randomized subject (and their caregiver, if applicable) will receive instructions on the SC infusion pump and SC infusion technique. Training on SC infusion through the use of video and/or verbal instruction should first be discussed with the subject during Screening to familiarize the subject with the SC infusion procedure before randomization. Site staff should recommend the weekly dosing regimen based on the subject's weight, ie, number of SC infusions needed to deliver the total volume in 1 week. The Crono Pump should be programmed by the site staff with the correct volume based on body weight before the study visit ends. The programmed pump volume should be confirmed at every study visit.

The subject will be trained at the study site at the Week 1 Visit and Week 2 Visit by the site staff. Retraining of the subject or caregiver at the site is permitted for an additional 2 weeks

(Week 3 and Week 4), only if the subject or caregiver experiences difficulty with the SC infusion technique. Additional trainings needed beyond Week 2 will be documented in the eCRF. No other study procedures are required to be performed at these additional SC infusion trainings. If the subject or caregiver still is not able to administer the SC infusions at home by Week 4, the subject will be withdrawn from treatment and encouraged to continue study assessments to Week 25 (EOP1).

Detailed information on the home storage, preparation, and SC infusion of IMP will be provided in the IMP manual.

The CRONO S-PID 50 Pump will be provided to deliver the SC infusions to the subject. Refer to the IMP manual and the CRONO Pump user guide for further details on the device.

5.1.3.1 Dosing Modification

Modifications of IMP dose are not permitted.

5.1.3.2 Treatment Compliance

Subjects will record details of their infusion in the diary including whether the caregiver assisted in the SC infusion. In addition, subjects will bring all of their used/partially used vials of IMP to the study site at every study visit. Treatment compliance will be monitored based on review of the diary data and the number of returned vials, the results of which will be documented.

5.1.3.3 Overdose

Overdose is defined as the accidental or intentional infusion or ingestion of any dose of a product that is considered excessive. The effects of any potential overdose with IgPro20 have not been studied. See Section 9.6.5 for IMP overdose reporting requirements.

5.1.4 Packaging, Labeling, Supply and Storage

5.1.4.1 Packaging and Labeling

IMP will be packaged and labeled according to current ICH GMP and GCP guidelines and national legal requirements. Specific details regarding packaging of IMP are provided in the IMP manual.

5.1.4.2 Supply and Storage

IMP will be supplied to the study sites by CSLB or delegate.

Refer to Section 5.1.1 and Section 5.1.2 for IMP site storage instructions. Subjects will be required to place IMP in home refrigerators for storage. Storage details will also be included in the IMP manual provided to the sites and the subjects.

5.2 Accountability and Destruction

IMP must be used only as directed in the clinical study protocol.

The investigator (or delegate) will confirm receipt of all shipments of IMP (IgPro20 and placebo) in the IRT system. All supplies of IMP must be accounted for throughout the study. Records for the delivery of IMP to the study site, the inventory at the study site, the use by each subject, and the destruction or return of IMP to CSLB/designee must be maintained by the investigator (or delegate) using the appropriate form or IRT system. The investigator (or delegate) must provide reasons for any discrepancies in drug accountability.

For Japan sites only, drug inventory and accountability logs/reports must be dated and signed by the head of the medical institute or the study drug storage manager (if assigned by the head of medical institute). The study drug storage manager may delegate the tasks to the responsible hospital pharmacists.

Further details regarding accountability and destruction of IMP are provided in the IMP manual.

5.3 Other Interventions

5.3.1 Oral Rescue Corticosteroid Treatment

In the event of clinical worsening (eg, subject meets DOW criteria) between Week 9 and Week 25, the investigator may decide that the subject requires oral rescue corticosteroid treatment for recovery. Intravenous pulse rescue corticosteroid treatment is not permitted.

In this case, the following guidance applies:

1 Oral rescue corticosteroid treatment should be given only if DOW criteria are met.

2 The earliest that oral rescue corticosteroid treatment can be given is Week 9, to allow for IMP steady state to be achieved. The DOW consists of meeting 1 of the following 3 criteria on 2 consecutive study visits at least 2 weeks apart, up to Week 25:

a) Physician Global Disease Activity Assessment VAS worsening ≥ 2 cm* and MMT-8 worsening ≥ absolute 10%, - OR -

b) Extramuscular Global Assessment VAS worsening ≥ 2 cm, - OR -

c) Any 3 of 6 CSMs (see Section 3.3.1) worsening by ≥ absolute 20%

* If baseline Physician Global VAS is 8 to 10, then any worsening on Physician Global VAS is acceptable as long as MMT-8 criterion is met.

3 The rescue oral corticosteroid (prednisolone equivalent) treatment should be provided as per the Treating Physician's (see Table 7) standard of care but should not exceed 1 mg/kg/day for up to 5 days.

4 It is recommended that after oral rescue corticosteroid treatment, the oral corticosteroid dose be returned to Baseline dose by Week 25, if clinically possible.

Clinical worsening according to DOW is finished at the first subsequent study visit where none of the criteria are met. A potential next DOW and possible rescue oral corticosteroid treatment can start only after the end of the preceding DOW.

Oral rescue corticosteroid treatment is not permitted in Study Period 2. During Study Period 3, the use of additional oral corticosteroid treatment is permitted. Prior to increasing corticosteroids, investigators should verify that subjects are still benefiting from treatment with IgPro20.

Consequence of oral rescue corticosteroid treatment during Study Period 1

The subject will be classified as a non-responder at Week 25 but will continue the study as long as the subject remains on IMP treatment.

5.3.2 Concomitant Oral Corticosteroid Tapering

The permitted ≤ 20 mg/day concomitant oral corticosteroid (prednisolone equivalent) dose must be tapered starting at Week 17 if the subject has demonstrated clinically relevant improvement, ie, ≥ 2 cm improvement on the 10-cm Physician Global Disease Activity Assessment VAS. The taper regimen to be followed depends on the subject's previous stable corticosteroid dose:

a) If stable dose is 11 to 20 mg/day oral prednisolone equivalent, decrease dose by 2.5 mg/day every 2 weeks, as tolerated, to 10 mg, then by 1 mg/day every 2 weeks as tolerated

b) If stable dose is ≤ 10 mg/day, taper by 1 mg/day every 2 weeks as tolerated

If lowering the dose of corticosteroids results in an increase in symptoms that does not meet criteria for oral corticosteroid rescue treatment but in the judgement of the Treating Physician requires response, it is permissible to increase the dose of concomitant oral corticosteroid to up to 125% of the Baseline corticosteroid dose; only an increase to doses greater than 125% of the Baseline corticosteroid dose following corticosteroid taper starting at Week 17 will be considered a "rescue" corticosteroid dose. Once clinical stabilization has occurred, the taper schedule will resume (ie, taper will continue to a dose in which the subject remains stable).

5.3.3 Access to IMP after the End of Study Participation

Subjects will not be provided with IMP by CSLB after completion or discontinuation from the study.

6 Allocation to Treatment

6.1 Subject Assignment

After providing written informed consent, the subject will be issued with a study-level unique subject identification number via an IRT system. The subject identification number will be used to identify the subject for the duration of the study. Subject identification numbers will not be reassigned. If a subject is rescreened, the original subject identification number will be used.

6.2 Randomization Procedures

Eligible subjects will be randomized to 1 of the 2 double-blind treatment sequences by means of IRT. The IRT will assign the IMP to each subject and the correct dose volume based on the subject's body weight. Randomization will be done centrally and CSLB will supply the investigator with a user guide for the IRT.

Randomization will be stratified by region (Japan vs. non-Japan) and by MMT-8 assessment (≤ 142 points vs. > 142 points) to ensure even distribution of subjects to treatment sequences within stratum. For subjects with MMT-8 score at Baseline of ≤ 142 points and a muscle group not able to be assessed because of a non-DM related injury or an amputation, the Evaluating Physician will need to determine the appropriate stratification according to DM with muscle weakness (classic DM, ≤ 142 points) or DM with little or no muscle weakness (hypo/amyopathic DM, > 142 points) and assign appropriate stratum for this subject.

The randomization list will be generated by the IRT external service provider according to the approved randomization specifications. The IRT external service provider will keep the randomization code on file.

6.3 Blinding Procedures

6.3.1 Blinding Method

Throughout the study, the IMP will be dispensed in 50-mL vials in blinded packaging that ensures IgPro20 will not be distinguishable from the placebo.

Adequate procedures are in place to ensure the integrity of the blinded data within CSLB. Study data will be provided to the IDMC as unblinded data, as requested. These procedures are outlined in the IDMC Charter and a separate Study Blinding/Unblinding Procedures document.

Serum IgG levels will not be disclosed to the investigative site or any blinded study personnel before unblinding the study.

6.3.2 Breaking the Blind for an Emergency

The randomization code for individual subjects may be unblinded to a site during the study in emergency situations for reasons of subject safety, if knowing treatment assignment will change subject management. In case of an emergency situation for the reason of subject safety, the investigator should use the IRT to identify the treatment allocation for a subject. Whenever possible, the investigator should consult with CSLB before unblinding the

randomization code. The reason for unblinding the randomization code must be fully recorded in the subject's source documents, and the investigator must follow the defined procedures provided in the study reference manuals. The subject's treatment allocation should not be recorded in the subject's source document.

6.3.3 Planned Unblinding Procedures

CSLB will authorize that the study be unblinded for analysis after all subjects have completed all assessments for Study Period 1 and the data has been cleaned for primary data analysis:

- CSLB employees will be blinded to treatment allocation until all subjects have completed all assessments for Study Period 1 and the data has been cleaned for primary data analysis. Site monitors will remain blinded to treatment allocation until all subjects have completed all assessments for Study Period 2.
- Subjects and caregivers, as well as site personnel involved in the conduct of the study, will be blinded to treatment allocation until all subjects have completed all assessments for Study Period 2.

6.3.4 Ad hoc Safety Unblinding

CSLB's Global Clinical Safety and Pharmacovigilance personnel may, on an ad hoc basis, unblind the randomization code directly in the IRT at any time during the study because of a safety concern. The purpose of the unblinded data review is to determine if there is a risk to subject safety that would require further action either for the individual management of a study subject or for the ongoing conduct of the study. The need to unblind a subject or group of subjects may not necessarily arise because of an SAE. The need to unblind on an ad hoc basis will be determined by CSLB's Global Clinical Safety and Pharmacovigilance.

7 Contraindications, Permitted Therapies and Prohibited Therapies

7.1 Contraindications and Precautions to Further Dosing

IgPro20 is contraindicated in IgA-deficient patients with antibodies against IgA and with a history of severe systemic hypersensitivity or anaphylactic reactions/anaphylaxis to the active substance of IgPro20 or to any of its excipients (L-proline stabilizer and polysorbate 80).

IgPro20 must not be administered if hyperprolinemia type I or II condition exists [IgPro20 IB].

7.2 Permitted Therapies

The following therapies are PERMITTED during the study (note: this list is not intended to be all inclusive) provided a stable dose/regimen has been achieved according to the designated time period (in parentheses) before Baseline:

- Prednisolone equivalent (≤ 20 mg/day, except for oral rescue corticosteroid treatment [Table 6]), topical corticosteroids (low to medium potency), inhaled corticosteroids, topical immunosuppressants, physiotherapy (1 month). Taper of concomitant oral corticosteroid dose is required starting at Week 17 if the subject has demonstrated clinically relevant improvement (see Section 5.3.2). Monitoring for corticosteroid side effects should continue (see Section 8.1.2.1).

Table 6 Corticosteroid Dose Equivalency

Corticosteroid	Equivalent Dose	Corticosteroid	Equivalent Dose
Prednisolone	20 mg	Betamethasone	2.4 mg
Prednisone	20 mg	Dexamethasone	3.0 mg
Methylprednisolone	16 mg	Hydrocortisone	80 mg
Triamcinolone	16 mg	Cortisone	100 mg

Source: Farinde, 2019; values in source were multiplied by 2 to equal 20 mg prednisolone dose.

- Antimalarial agents, eg, hydroxychloroquine, chloroquine (3 months)
- Systemic immunosuppressives or disease-modifying antirheumatic drugs, eg, azathioprine, methotrexate, mycophenolate, cyclosporine, tacrolimus (3 months)

Doses of stable permitted therapy (including corticosteroids) may be reduced or discontinued after enrollment because of side effects, abnormal laboratory values, or concurrent illness. No other change to permitted concomitant therapy, with the exception of taper of corticosteroid dose starting at Week 17 (see Section 5.3.2), is allowed during Study Periods 1 and 2.
In Study Period 3, doses of stable concomitant medication may be decreased based on subject status.

7.3 Prohibited Therapies

The following therapies are NOT PERMITTED during the study and require a minimum washout period (in parentheses) before Baseline if discontinued:

- IM, IV, or intra-articular corticosteroids including adrenocorticotropic hormone (1 month)
- IgG (up to 2 months [Note: Subject may enroll before the end of the 2 month washout period if clinical deterioration is experienced after withdrawal of IgG.])
- Plasma exchange or plasmapheresis (3 months)
- Cyclophosphamide or alkylating agents (6 months)
- Other biologic therapies including investigational agents (6 months or 5 half-lives, whichever is longer)
- Rituximab or other B cell depleting therapies (9 months or evidence of persistent B cell depletion after stopping therapy)

Subjects will not be enrolled into the study if they receive any prohibited therapy or any therapy in a prohibited dosage that cannot be discontinued or reduced to a permitted dose before Baseline.

7.4 Lifestyle Restrictions

7.4.1 Physical Activity

During study participation, there are no restrictions on the subject's normal physical activity, but subjects should not change their physiotherapy regimen from at least 1 month before Baseline to Week 17. After completing Week 17, the subject's physiotherapy regimen can be modified if clinically relevant improvement is achieved; however, any changes should be documented in the subject's eCRF. During Study Period 3, there are no restrictions with regard to physiotherapy.

7.4.2 Contraception

Female subjects of childbearing potential or male subjects must use a medically reliable form of contraception for the study duration and for 30 days after the last SC infusion of IMP. Acceptable methods of contraception are:

- Abstinence where local law permits abstinence as a contraception method and where abstinence is the preferred and usual lifestyle of the subject, including refraining from heterosexual intercourse during the entire period of risk associated with the IMP
- Hormonal methods associated with inhibition of ovulation. Acceptable hormonal methods include: oral contraceptives, contraceptive medication patch, contraceptive medication injection, estrogen/progestin vaginal ring, or contraceptive medication implant
- At least 2 barrier methods. For example, female or male condoms with spermicidal foam or spermicidal jelly, or diaphragm with spermicidal foam or spermicidal jelly. The female condom and male condom should not be used together
- Use of intrauterine device (placed more than 3 months before providing informed consent)
- Bilateral tubal occlusion of female subjects (3 months before providing informed consent)
- Vasectomy of male subjects or male partners/spouses of monogamous female subjects (3 months before providing informed consent)

Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are **NOT** acceptable definitions of contraception.

8 Study Procedures and Visit Schedule

8.1 Clinical Procedures

The timing and frequency of the clinical procedures described in the following sections are detailed in the Schedules of Assessments. More frequent assessments may be performed at unscheduled visits if clinically indicated, at the discretion of the investigator. Refer to the provided study manuals for detailed instructions on how and when the scheduled and unscheduled assessments should be performed.

8.1.1 Handling of Study Assessments

During Study Period 1 and Study Period 2, sites should provide at least 2 physicians for study related assessments: a “Treating Physician” and an “Evaluating Physician.” The Treating Physician will be the primary contact for the subject and will be responsible for all safety and

treatment-related tasks (Table 7). It is recommended that the Treating Physician be the Principal Investigator for the study. Tasks assigned to the Treating Physician may be delegated to other qualified site staff according to site general practice. The Evaluating Physician will be responsible for efficacy assessments and the review of all subject-entered data (Table 7); these tasks may not be delegated. At Baseline before randomization, the Treating and Evaluating Physicians should review and confirm the subject's DM status, to confirm that no clinically relevant improvement has occurred since Screening (see Section 8.5.3.1), and final eligibility.

In Study Period 3, it is recommended that the Evaluating Physician continues the assessments, if at all possible.

Training for all CSMs and other efficacy assessments will be provided to ensure that the assessments made are attributable to DM and not to other disease. The training will also include detailed instructions on how to complete the assessments. The Treating and Evaluating Physicians should remain the same for each subject through all study visits. Training will be provided to ensure consistency in safety and efficacy assessments in the event that 1 of the physicians is not available for a study visit. The Treating Physician will be notified when the subject has met the criteria for DOW, so that appropriate steps regarding the subject's status per protocol can be implemented. The Treating Physician will have the responsibility to provide the final eCRF signature for each subject.

Table 7 Role Responsibilities for Study Assessments

Treating Physician	Evaluating Physician	Subject
• Informed consent	• Timed Up and Go	• EQ-5D-5L
• EULAR/ACR criteria	• CDASI	• TSQM-9
• Physician Global Damage Assessment	• MMT-8	• WPAI-PH
• Eligibility	• MDAAT[A]	• HAQ
• Medical/Surgical history		• 5-D Itch (Pruritus)
• DM treatment history		• Patient Global Activity
• General physical exam		• SC Infusion Diary
• Height and body weight		
• 12-lead ECG		
• Vital signs		
• All laboratory collections		
• AEs		
• Concomitant therapies		
• Physiotherapy documentation		
• SC infusion training		
• Randomization/IRT		
• SC Infusion Diary review		
• IMP dispensing/accountability		
• Rescue corticosteroid treatment[B]		
• Withdrawal decision		
• Safety assessments[C]		

5-D = 5-Dimension; AE = adverse event; CDASI = Cutaneous Dermatomyositis Disease Area and Severity Index; CSMs = Core Set Measures; DM = dermatomyositis; DOW = Definition of Worsening; DVT = deep vein thrombosis; ECG = electrocardiogram; eCOA = Electronic Clinical Outcomes Assessment; EQ-5D-5L = EuroQoL 5-Dimension Questionnaire; EULAR/ACR = European League Against Rheumatism/American College of Rheumatology; HAQ = Health Assessment Questionnaire; IMP = investigational medicinal product; IRT = Interactive response technology; MDAAT = Myositis Disease Activity Assessment Tool; MMT-8 = manual muscle testing of 8 muscle groups; PE = pulmonary embolism; SC = subcutaneous; TEE = thromboembolic event; TIS = Total Improvement Score; TSQM-9 = Abbreviated Treatment Satisfaction Questionnaire for Medication; WPAI-PH = Work Productivity and Activity Impairment Questionnaire for General Health.

A MDAAT includes **Extramuscular Global Assessment** and **Physician Global Disease Activity** components, 2 of the CSMs used for TIS and DOW calculations. The DOW calculation is performed by the eCOA solution and available for Treating Physician assessment of subject's need for rescue corticosteroid treatment.

B Rescue corticosteroid treatment can only be administered if DOW has been met.

C Safety assessments include monitoring for corticosteroid treatment, monitoring for TEEs (including Wells' Criteria for DVT and/or Wells' Criteria for PE), monitoring for hemolysis at Week 2 and Week 5.

8.1.2 Demographics and Safety Assessments

Subject demographics and safety assessments to be conducted during this study are provided in Table 8. Clinical laboratory assessments are to be performed at time points as detailed in the Schedule of Assessments. The time windows for each type of assessment are detailed in Table 14.

Table 8 Study Procedures: Demographics and Safety Assessments

Assessment	Description
Medical/surgical history	• Diagnosis and disease status • Relevant medical/surgical history, including DM history details • DM treatment history • Current/concomitant therapies • Contraception method (if relevant)
Demographics	Age, sex, race, and ethnicity (where permitted)
Physical examination	As per the site's standard procedure, including height and Physician Global Damage Assessment only at Screening
12-lead ECG	As per the site's standard procedure
Safety assessments	Refer to Section 8.1.2.1 (Monitoring for Corticosteroid Treatment), Section 8.1.2.2 (Monitoring for Thromboembolic Events), and Section 8.1.2.3 (Monitoring for Hemolysis Risk Assessment)
Adverse events	Refer to Section 9 (Adverse Events)
Body weight	As per the site's standard procedure
Waist circumference	As per the site's standard procedure
Vital signs	• Blood pressure (systolic and diastolic) • Pulse rate (per minute) • Respiratory rate • Body temperature
Pregnancy test[A]	Serum test at Screening and urine test at all other assessments for hCG, as indicated for premenopausal females capable of becoming pregnant
Thrombophilic Abnormality Screen[B]	• Protein C • Protein S • Lupus anticoagulant • Prothrombin G20210A mutation • Antithrombin III • Cardiolipin antibodies • Factor V Leiden mutation
Hematology	• ABO blood group • Rh factor • $HbA1_c$ • Hemoglobin • Hematocrit • Blood cell counts: erythrocytes, leukocytes with differential counts (neutrophils, basophils, eosinophils, lymphocytes, monocytes), platelets
Muscle enzymes	• CK • AST • Aldolase • LDH • ALT
Hemolysis	• DAT • Total bilirubin • Direct bilirubin • Indirect bilirubin • Haptoglobin • Reticulocytes • Peripheral blood smear[C]
Other biochemistry	• Alkaline phosphatase • Bicarbonate • BUN • Chloride • GGT • Sodium • Glucose • Potassium • Creatinine

Assessment	Description
Coagulation	• D-dimer
Virus serology	Blood samples are to be tested for HBsAg, HCV antibodies, and HIV-1, HIV-2 antibodies

ABO = blood group type A, type B, type AB, or type O; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; DAT = direct antiglobulin test; DM = dermatomyositis; ECG = electrocardiogram; GGT = gamma-glutamyl transferase; $HbA1_c$ = glycated hemoglobin; HBsAg = hepatitis B virus surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; Rh = Rhesus.

A Serum/urine pregnancy test is to be completed for all females of reproductive potential. A female of reproductive potential is defined as a premenopausal female capable of becoming pregnant. This includes women on oral, injectable, or mechanical contraception and women whose partners have been vasectomized or have received or are utilizing mechanical contraceptive devices.

B Known deficiencies in proteins C, protein S, and antithrombin-III levels and presence of lupus anticoagulant/cardiolipin antibodies (antiphospholipid antibodies) and/or the 2 gene mutations (Prothrombin G20210A and Factor V Leiden) will exclude a subject from the study (Section 4.1.2, Exclusion Criterion 6).

C Peripheral blood smear will only be analyzed for a drop in hemoglobin from the previous study visit ≥ 1 g/dL.

Results of laboratory tests should be signed and dated in a timely manner and retained at the study site as source data. Refer to Section 9 for information on how AEs based on laboratory tests should be assessed and reported.

8.1.2.1 Monitoring for Corticosteroid Treatment

For subjects receiving concomitant corticosteroids, the Treating Physician should continue the monitoring and management of corticosteroid treatment at every study visit according to current standard of care and as recommended by the protocol. It is anticipated that subjects in the study were previously on corticosteroids that have been reduced to prednisolone equivalent 20 mg/day or less at least 1 month before Baseline. Further dose reduction (taper) must be started at Week 17 if clinically relevant improvement (see Section 3.1) has been achieved. Subjects with clinical worsening in Study Period 1 (eg, subject meets DOW criteria) will be eligible for oral corticosteroid rescue treatment of up to prednisolone equivalent 1 mg/kg daily for up to 5 days to be given at the discretion of the Treating Physician. Corticosteroids are known to be associated with a variety of side effects in a dose- and duration-of-treatment-dependent manner [Oray et al, 2016]. Please refer to Section 5.3.1 for more information on rescue treatment. Reporting of AEs related to corticosteroid treatment should be handled according to Section 9.2.

8.1.2.2 Monitoring for Thromboembolic Events (TEEs)

To reduce the risk of potential TEEs, this study excludes specific patient groups (Section 4.1.2, exclusion criterion 6 items pertaining to TEE risk). Nevertheless, TEE risk will be continuously monitored during the study.

The Treating Physician will assess the subject for the suspicion of a TEE per standard of care at every study visit during all Study Periods.

If there is suspicion of DVT or PE during Study Periods 1 or 2, the Wells' Criteria for DVT (Table 9) or Wells' Criteria for PE (Table 10) will be assessed and entered in the eCRF [Modi et al, 2016; Wells' Criteria for DVT; Doherty, 2017; Wells' Criteria for Pulmonary Embolism].

A score of > 1 on the Wells' Criteria for DVT requires diagnostic imaging (lower extremity ultrasound) to rule out DVT. A score of > 1 on the Wells' Criteria for PE requires additional imaging, (eg, computerized tomography scan, ventilation/perfusion scan, pulmonary angiography, or other modalities) be performed as per the site's standard of care.

When a diagnosis of DVT or PE is confirmed, IMP treatment must be discontinued; however, the subject may continue in the study for other study assessments up until Week 53. During Study Period 3, there will be no formal assessment of Wells' Criteria. TEEs will be monitored as part of standard assessment for AEs at each monthly site visit. If a TEE occurs during participation in Study Period 3, the subject must be discontinued from the study.

Table 9 Wells' Criteria Scoring for Suspicion of DVT

Assessment	Score
Active cancer (Treatment or palliation within 6 months)[A]	+1
Bedridden recently > 3 days or major surgery within 12 weeks[A]	+1
Calf swelling > 3 cm compared to the other leg (Measured 10 cm below tibial tuberosity)	+1
Collateral (nonvaricose) superficial veins present	+1
Entire leg swollen	+1
Localized tenderness along the deep venous system	+1
Pitting edema, confined to symptomatic leg	+1
Paralysis, paresis, or recent plaster immobilization of the lower extremity	+1
Previously documented DVT[A]	+1
Alternative diagnosis to DVT as likely or more likely	-2
Total Score	

DVT = deep vein thrombosis.
A Exclusion Criterion (see Section 4.1.2)

Table 10 Wells' Criteria Scoring for Suspicion of PE

Assessment	Score
Clinical signs and symptoms of DVT	+3
PE is #1 diagnosis OR equally likely	+3
Heart rate > 100 bpm	+1.5
Immobilization at least 3 days OR surgery in the previous 4 weeks[A]	+1.5
Previous, objectively diagnosed PE or DVT[A]	+1.5
Hemoptysis	+1
Malignancy with treatment within 6 months or palliative[A]	+1
Total Score	

DVT = deep vein thrombosis; PE = pulmonary embolism.
A Exclusion Criterion (see Section 4.1.2)

All TEEs, including but not limited to DVT and PE, will be classified as AESIs (see Sections 9.1.3 and 9.6.2). Follow-up monitoring and treatment (eg, anticoagulation) will be performed according to the site's standard of care using established guidelines (eg, American Society of Hematology 2018).

8.1.2.3 Monitoring for Hemolysis

For determination of hemolysis, an assessment of clinical signs of hemolysis will be performed at Week 2 and Week 5 and compared to Baseline. In combination with laboratory results confirmed or suspected hemolysis cases will be defined as follows:

Confirmed hemolysis:

Subjects fulfilling criterion A and at least 2 of criteria B, where 1 of the minor criteria must be direct antiglobulin test (DAT) positive after infusion and within 28 days of the first IMP infusion, will be considered to have "confirmed hemolysis." Confirmed hemolysis will be reported as an AE.

Suspected hemolysis:

Subjects fulfilling criterion A and at least 1 of criteria B will be considered to have "suspected hemolysis."

- Criterion A

  Drop in hemoglobin of > 1 g/dL since the time of first administration of IMP without clinical evidence of blood loss from gastrointestinal bleeding, menorrhagia, hemoptysis, major hematoma, or injury and not explained by repeated phlebotomy

- Criteria B

  Presence of minor criteria documented since the time of first administration of IMP, consisting of:
  - DAT positive
  - Haptoglobin < lower limit of normal
  - LDH > ULN
  - Total or indirect (unconjugated) bilirubin > ULN or jaundiced
  - Hemoglobinuria or red/dark urine
  - Hemoglobinemia
  - Spherocytosis
  - Hepatosplenomegaly

If AE of hemolysis is reported, it must be graded by the investigator:

- Grade 1 – Laboratory evidence of hemolysis only (eg, DAT positive, schistocytes, decreased haptoglobin)
- Grade 2 – Clinical evidence of hemolysis and ≥ 2 g/dL decrease in hemoglobin
- Grade 3 –Transfusion or medical intervention indicated (eg, steroids)
- Grade 4 – Life-threatening consequences; urgent intervention indicated
- Grade 5 – Death

8.1.3 ANA, MSA, and MAA Assessments

Additional blood samples for presence of ANA, MSA, and MAA will be collected at Screening, Week 25, and Week 53 (Table 11).

The following MSA will be analyzed: anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-SRP, anti-Mi-2, anti-p155/140, anti-TIF-1γ, anti-MDA5, anti-NXP-2, anti-HMGCR, anti-SAE-1Ab.

The following MAA will be analyzed: anti-PM/Scl, anti-Ro-SSA, anti-Ku, anti-U1 RNP, anti-U3 RNP.

The samples for ANA, MSA, and MAA will be analyzed by the central laboratory (ANA) and a specialized reference laboratory (MSA and MAA).

Table 11 Clinical Procedures: ANA, MSA, and MAA Assessments

Procedure	Description
ANA, MSA, and MAA assessments	Blood samples will be collected for ANA, MSA, and MAA assessments

ANA = antinuclear antibody; MAA = myositis-associated autoantibodies; MSA = myositis-specific autoantibodies.

8.1.4 Pharmacokinetic Assessments

Trough serum samples for IgG level determination will be collected at Screening and at specified study visits (Table 12).

Additional blood samples for rich PK sampling of IgG levels will be collected at Week 37 (Study Period 2). Rich PK samples will be collected from up to 10 Japanese subjects and 30 non-Japanese subjects. The Week 37, 168-hour rich PK blood sample must be drawn before start of Week 38 dose infusion. The additional samples will be collected at the times listed in Table 14. Blood draws for rich PK samples may be drawn by a phlebotomist at the subject's home where available and/or allowed by local law.

The samples for serum IgG concentrations will be analyzed by the central laboratory by immunoturbidimetry. Serum IgG levels will not be disclosed to the investigative site or any blinded study personnel prior to unblinding the study. See Schedule of Assessments for Rich Pharmacokinetic Sampling for details.

Table 12 Clinical Procedures: Pharmacokinetic Assessments

Procedure	Description
Pharmacokinetics evaluations	Blood samples will be collected for IgG level determination

IgG = immunoglobulin G.

8.1.5 Efficacy Assessments

Efficacy assessments are to be performed by the Evaluating Physician and the subject at time points as detailed in the Schedule of Assessments. The time windows for each type of assessment are detailed in Section 8.5.1.

IMACS 6 CSMs:

Patient Global Activity Assessment: The subject will assess his/her global DM disease activity at the study visit by selecting a point on a 10-cm line with "No evidence of disease activity" on the left and "Extremely active or severe disease activity" on the right. For details, see Appendix 5.

Manual Muscle Testing of 8 Muscle Groups (MMT-8): The Evaluating Physician will assess the MMT-8. The 8 muscles to be tested are 1 axial muscle group - neck flexors; and 7 bilateral muscles - proximal: deltoid middle, biceps brachii, gluteus maximus, gluteus medius, and quadriceps; and distal: wrist extensors and ankle dorsiflexors. DM subjects with muscle weakness (classic DM) will have MMT-8 scores ≤ 142 points and DM subjects with little or no muscle weakness (hypo/amyopathic DM) will have MMT-8 scores > 142 points. For subjects with a muscle group not able to be assessed because of a non-DM related injury or an amputation at Baseline, the Evaluating Physician will determine the appropriate muscle weakness stratum for this subject. For details, see Appendix 6.

Health Assessment Questionnaire (HAQ): The subject will answer a series of questions which assess how DM is affecting 8 activities of daily living: dressing/grooming, arising (position changes), eating, walking, hygiene, reach, grip, and activities, eg, running errands, chores. For details, see Appendix 7.

Muscle Enzyme: The most abnormal muscle enzyme (CK, LDH, AST, ALT, or aldolase) at Baseline will be assessed for changes during Study Period 1 and Study Period 2. If all muscle enzymes are within normal range at Baseline, the most abnormal enzyme will be determined by considering the value in relation to the ULN range. If more than one muscle enzyme has the same highest abnormality score at Baseline, the most abnormal muscle enzyme will be chosen according to the following priority list: CK, LDH, AST, ALT, aldolase. For details, see Appendix 8.

Myositis Disease Activity Assessment Tool (MDAAT) for Physician Global Disease Activity and Extramuscular Global Assessment: The MDAAT is a combined tool which will capture the Evaluating Physician's assessment of disease activity of various organ systems using a 0 to 4 point scale as well as a VAS for each disease activity component. There are 7 extramuscular disease activity components (Constitutional, Cutaneous, Skeletal, Gastrointestinal, Pulmonary, Cardiovascular, Other [specify]) and a muscle disease activity component, each with an accompanying VAS. Additionally, an **Extramuscular Global Assessment** VAS and a **Physician Global Disease Activity** VAS will be assessed. **Extramuscular Global Assessment** and **Physician Global Disease Activity** components are the 2 CSMs used for TIS and DOW calculations. In Study Period 3, only the Physician Global Disease Activity VAS will be collected. For details, see Appendix 4.

Other Measures:

Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI): The Evaluating Physician will assess 4 disease areas (Extent [anatomical locations], Gottron's Hands, Periungual, and Alopecia) for activity and damage and provide a total score for each. For details, see Appendix 9.

Timed Up and Go: The Evaluating Physician will measure how quickly the subject can rise from a sitting position, walk 3 meters, and return to same sitting position in Study Period 1 and Study Period 2. For details, see Appendix 11.

8.1.6 Other Assessments

8.1.6.1 Disease Specific

Physician Global Damage Assessment: At Screening only, the Treating Physician will rate the global (overall) assessment of current DM disease damage by using a 5-point Likert scale (0 to 4). This global assessment is to be performed using all information available to the Treating Physician at Screening, including the subject's appearance, history, physical examination, diagnostic laboratory testing, and the resultant medical therapy. For details, see Appendix 3.

8.1.6.2 Non-disease Specific

5-D Itch (Pruritus) Score: Subjects will assess 5 dimensions of itch history in Study Period 1 and Study Period 2: Duration, Degree (intensity), Direction (better or worse from previous month), Disability of 4 activities of daily living, and Distribution (location[s] on body). For details, see Appendix 10.

EuroQoL 5-Dimension Questionnaire (EQ-5D-5L): The subject will select which best describes his own health state at the study visit in the following 5 dimensions: Mobility, Self-care, Usual Activities, Pain/discomfort, and Anxiety/depression. The subject will also select a point on a scale drawn like a thermometer to indicate how good or bad the health state is, with best state as "100" and worst state as "0." For details, see Appendix 12.

Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH): The subject will answer questions about the effect of his/her health on the ability to work or perform regular activities in Study Period 1 and Study Period 2. General health is defined as any symptoms relating to physical or emotional well-being. For details, see Appendix 13.

Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9): The TSQM-9 is a 9-item general instrument that measures the major dimensions of satisfaction with a medication [Bharmal et al, 2009]. Scores on the TSQM-9 range from 0 (indicating poor satisfaction) to 100 (indicating perfect satisfaction). This instrument usually requires less than 5 minutes for subject completion and was developed to be used with any medication and across cultural and different language settings. Scores on the Effectiveness (3 items), Convenience (3 items), and Global Satisfaction (3 items) scales will be assessed in a cross-sectional manner in Study Period 1 and Study Period 2. For details, see Appendix 14.

8.1.6.3 Exploratory Biomarkers

Blood samples will be collected and stored to assess exploratory biomarkers in DM for a separate, future study (Table 13). These exploratory assessments may include but will not be limited to the following: chemokines, cytokines, complement, and protein expressions, DNA, RNA, and messenger RNA. Sample collection for exploratory evaluation of biomarkers will be clearly mentioned in the ICF for this study. Sample collection for DNA testing is optional for all subjects and will require a separate consent. These potential DM biomarkers may allow for better understanding of prognosis, disease course, and correlation to treatment in DM subjects and, therefore, might allow for individualized treatment. The exploratory nature of these analyses precludes the use of the results to predict future risk or to inform health care. None of the 59 genes of potential high medical importance which appear on the American College of Medical Genetics list of published recommendations for reporting of incidental findings will be examined. Therefore, neither the investigator nor the subject will be informed of these results (DNA, RNA, or serum proteins).

In order to understand how the biomarker results might inform on these aspects of DM, they will need to be correlated with the subject's treatment in the study, gender, ethnicity, age, hematology, serum chemistry, serum IgG, efficacy and quality of life assessments. Assays will be performed in-house at CSL laboratories and by external service providers. The CSL laboratory is located at 30 Flemington Road, Parkville, Victoria 3052, Australia. DNA samples require anonymization by the central laboratory before transfer to CSL Australia for analysis at the end of the study. All biomarker samples will be retained for a maximum of 10 years.

Table 13 Clinical Procedures: Exploratory Biomarkers

Procedure	Description
Biomarker samples	Blood samples will be collected for exploratory biomarker assessments (serum and DNA and RNA analyses)

8.2 Blood Samples

During the study, blood will be taken from each subject for laboratory safety assessments, PK evaluations, ANA, MSA and MAA, exploratory biomarkers, and virology (HBV, HCV, and HIV) samples. Approximately 360.5 mL of blood will be drawn from each subject during Study Period 1 and Study Period 2. An additional 8 mL of blood per year of study participation will be collected during Study Period 3, with an additional 7.5 mL collected for virology retention at the EOP3 Visit, leading to a maximum of 392 mL collected over all 3 study periods. Detailed information on the volume of blood to be sampled for each assessment will be available in the ICF and laboratory manual.

Repeat or unscheduled blood samples may be taken for safety reasons or for technical issues with the samples and will be in addition to the estimated 392 mL blood volume for scheduled assessments.

Refer to the study manual for details about the collection, storage, handling and processing of blood samples.

8.3 Retention of Samples

Retention samples of serum for virology will be obtained as specified in the Schedule of Assessments. Virology retention samples will be stored at the central laboratory. In case of any evidence for a possible treatment-emergent virus infection within 1 year after study completion, the retention sample will be analyzed in the central laboratory.

All exploratory biomarker samples collected during the study will be retained and destroyed within 10 years after completion of the study. Biomarker retention samples will be stored at CSLB (30 Flemington Road, Parkville, Victoria 3052, Australia). Refer to the study manual for further details about the storage and destruction of retention samples.

8.4 Prior and Concomitant Therapies

All medications taken by a subject within 3 months before Baseline are considered prior therapy and must be documented in the eCRF.

Previous medications and therapies for DM that the subject has received within 1 year before Baseline must be documented in the eCRF. If possible, all available data regarding the subject's treatment with IgG therapy since being diagnosed with DM should be recorded in the subject's eCRF.

All drugs and/or procedures currently being administered to a subject at the time of signing informed consent, and which continue to be taken in addition to IgPro20 or placebo during the study, as well as drugs and/or procedures initiated after the first infusion of study product, are regarded as concomitant therapies and must be documented as such in the eCRF.

Any prohibited dose adjustments in permitted concomitant therapies (see Section 7.2) will lead to withdrawal from treatment.

8.5 Visit Schedule

8.5.1 Assessment Time Windows

The timing and frequency of the study visits are described in the Schedule of Assessments. Time windows for all assessments are detailed in Table 14.

Table 14 Time Windows for Assessments

Visit/Procedure	Time window (relative to scheduled visit/procedure)
Screening	Up to 2 months before Baseline
Week 2 and all subsequent study visits in Study Period 1 and Study Period 2	± 3 days
Monthly study visits in Study Period 3	± 7 days
Physical examination, to include Physician Global Damage Assessment only at Screening	Before first SC infusion on Week 1[A]
Vital signs, including body weight	Before first SC infusion on Week 1 and Week 2[A]
Urine collection for pregnancy test[B]	Before first SC infusion on Week 1[A]
Blood collection for laboratory tests	Before first SC infusion on Week 1 and Week 2[A]
Blood collection for rich PK (serum IgG and exploratory biomarkers)	Week 37, trough sample collection at study visit Week 37, 24 ± 3 h relative to the start of first infusion Week 37, 48 ± 3 h relative to the start of first infusion Week 37, 72 ± 3 h relative to the start of first infusion Week 37, 120 ± 3 h relative to the start of first infusion Week 37, 168 ± 3 h relative to the start of first infusion
Subject SC Infusion Diary review	At the end of SC infusions on Week 1 and Week 2[A]
Adverse event documentation	Before first SC infusion on Week 1 and Week 2[A]
Safety assessment documentation	Before first SC infusion on Week 1 and Week 2[A]

Visit/Procedure	Time window (relative to scheduled visit/procedure)
Concomitant therapy documentation	Before first SC infusion on Week 1 and Week 2[A]
Physiotherapy documentation	Before first SC infusion on Week 1 and Week 2[A]
Efficacy assessments	Before first SC infusion on Week 1 and Week 2[A]

h = hour; IgG = immunoglobulin G; PK = pharmacokinetic; SC = subcutaneous.

A For all other study visits, SC infusions are not performed at the study visit.

B Urine pregnancy test is to be completed for all females of reproductive potential.

8.5.2 Screening

All subjects must provide written informed consent before any study-specific assessments or procedures are performed (see Section 12.3).

The Screening examination must be performed no more than 2 months before the intended Baseline date. Note: A duration of 2 months may be required from last IgG dose to Baseline for subjects on IgG therapy before Screening (see Section 7.3). For subjects enrolling without active DM rash, the other objective evidence to confirm disease activity must be reviewed by CSLB medical monitoring staff (or delegate) before final eligibility is determined and the subject is randomized. The other objective evidence to confirm disease activity may include any of the following: MRI scan, electromyogram, muscle biopsy, or CK > 4 × ULN within 3 months before Baseline. If a potential subject fails eligibility for a reason other than DM diagnosis or disease activity, the potential subject may be rescreened 1 time for the study and all Screening assessments must be repeated.

The following procedures will be conducted and documented at the Screening Visit as specified in the Schedule of Assessments for Screening (Table 1):

- Obtain written informed consent and register the subject via IRT
- Relevant medical and surgical history to include DM history details (including age at first diagnosis) from time of diagnosis (available surgical history for the past 5 years), and prior treatments for DM
    - Available DM treatment history (eg, corticosteroids, other immunosuppressants, antimalarials, IgG [to include IgG details including type of therapy {eg, IV or SC}, method of administration {eg, central venous port, peripherally inserted central catheter}, dosage and frequency, and types of AEs experienced associated with the method of administration, since diagnosis])

- Documentation of previous age-appropriate cancer screening
- Demographics
- Review of inclusion and exclusion criteria including the EULAR/ACR classification criteria for DM
- CDASI
- General physical exam, including height
- 12-lead electrocardiogram (ECG)
- Body weight
- Vital signs
- Wells' Criteria
- Collection of blood sample for serum hCG pregnancy test, if applicable
- Collection of blood samples to assess the following:
  - Serum IgG level
  - Hematology
  - ABO blood group (blood group type A, type B, type AB, or type O) and Rhesus (Rh) factor
  - Muscle enzymes
  - Other biochemistry
  - Thrombophilic abnormality screen
  - Coagulation
  - ANA, MSA, and MAA
  - Virology
- Document AEs
- Document concomitant therapies
- Document physiotherapy
- Individual CSMs
- Physician Global Damage Assessment

If the subject is not eligible for the study, the primary reason for screen failure must be entered in the IRT.

8.5.3 Study Period 1

Study Period 1 is a 24-week, double-blind, placebo-controlled treatment period during which participating subjects receive either IgPro20 or placebo at 0.5 g/kg SC on a weekly basis. Study Period 1 starts with Baseline/Week 1 and continues through the Week 25 Visit (24 weeks ± 3 days after the first SC infusion of IMP). Study assessments will be performed as specified in the Schedule of Assessments for Study Period 1 (Table 2).

8.5.3.1 Baseline/Week 1

The Baseline and Week 1 visits occur at the same study visit; however, all Baseline procedures must be completed before the Week 1 procedures begin. The final eligibility criterion to be met is no clinically relevant improvement between Screening and Baseline (Section 4.1.2, Exclusion criterion 4). This determination will be made based on the Treating and Evaluating Physicians' clinical judgement following review of the efficacy assessments performed at Screening and Baseline.

Subjects who complete all Screening and Baseline CSM assessments and who fulfill all eligibility criteria (ie, eligible subjects) will be randomized. At the Baseline Visit, the following procedures are to be conducted and documented:

Baseline

- Confirm eligibility
- Randomization into double-blind treatment (see Section 6.2)
- General physical examination
- Body weight
- Waist circumference
- IMP assignment
- Vital signs
- Safety assessments
- Collection of urine sample for hCG pregnancy test, if applicable

- Collection of blood samples for virology retention and exploratory biomarkers (serum and DNA/RNA analyses)
- Collection of blood samples to assess the following:
  - Hematology
  - Glycated hemoglobin ($HbA1_c$)
  - Muscle enzymes
  - Hemolysis
  - Other biochemistry
  - Coagulation
  - Serum IgG
- Document AEs
- Document concomitant therapies
- Document any change to physiotherapy since the previous study visit
- Assess for clinically relevant improvement
- Individual CSMs
- CDASI
- 5-D Itch Score
- Timed Up and Go
- EQ-5D-5L, WPAI-GH

Week 1

- Document AEs
- Document concomitant therapies
- Training and supervision of first IMP SC infusion
- Supervision of subject SC Infusion Diary entry

8.5.3.2 Week 2

The following procedures will be conducted at 1 week ± 3 days after the first SC infusion of IMP:

- Body weight
- IMP assignment
- Vital signs
- Safety assessments
- Collection of blood samples to assess the following:
  - Hematology with peripheral blood smear
  - Hemolysis
  - Coagulation
  - Serum IgG
- Training and supervision of IMP SC infusion for Week 2
- Supervision of subject SC Infusion Diary entry
- Document AEs
- Document concomitant therapies
- Document any change to physiotherapy since the previous study visit

Starting with Week 3, the subject will adjust their first dosing day so that no SC infusions occur on the day of a study visit. Site instruction for this transition should be provided.

8.5.3.3 Week 5

The following procedures will be conducted at 4 weeks ± 3 days after the first SC infusion of IMP:

- Body weight
- IMP assignment
- Vital signs
- Safety assessments
- Collection of urine sample for hCG pregnancy test, if applicable

- Collection of blood samples for exploratory biomarkers (serum and RNA analyses)
- Collection of blood samples to assess the following:
  - Hematology with peripheral blood smear
  - Muscle enzymes
  - Hemolysis
  - Coagulation
  - Serum IgG
- Subject SC Infusion Diary review
- Document AEs
- Document concomitant therapies
- Document any change to physiotherapy since the previous study visit
- DOW assessment
- Individual CSMs
- CDASI

8.5.3.4 Week 9

The following procedures will be conducted at 8 weeks ± 3 days after the first SC infusion of IMP:

- Body weight
- IMP assignment
- Vital signs
- Safety assessments
- Collection of urine sample for hCG pregnancy test, if applicable
- Collection of blood samples for exploratory biomarkers (serum analysis)
- Collection of blood samples to assess the following:
  - Hematology
  - Muscle enzymes
  - Other biochemistry

- Coagulation
- Serum IgG

- Subject SC Infusion Diary review
- Document AEs
- Document concomitant therapies
- Document any change to physiotherapy since the previous study visit
- DOW assessment
- Individual CSMs
- CDASI
- 5-D Itch Score
- Timed Up and Go

8.5.3.5 Week 13

The following procedures will be conducted at 12 weeks ± 3 days after the first infusion of IMP:

- Body weight
- IMP assignment
- Vital signs
- Safety assessments
- Collection of urine sample for hCG pregnancy test, if applicable
- Collection of blood samples to assess the following:
  - Muscle enzymes
  - Coagulation
- Subject SC Infusion Diary review
- Document AEs
- Document concomitant therapies
- Document any change to physiotherapy since the previous study visit
- DOW assessment

- Individual CSMs
- CDASI
- EQ-5D-5L, WPAI-GH, TSQM-9

8.5.3.6 Week 17

The following procedures will be conducted at 16 weeks ± 3 days after the first SC infusion of IMP:

- Body weight
- IMP assignment
- Vital signs
- Safety assessments
- Collection of urine sample for hCG pregnancy test, if applicable
- Collection of blood samples for exploratory biomarkers (serum analysis)
- Collection of blood samples to assess the following:
  - Hematology
  - Muscle enzymes
  - Other biochemistry
  - Coagulation
  - Serum IgG
- Subject SC Infusion Diary review
- Document AEs
- Document concomitant therapies
- Assess if subject has clinically relevant improvement, and if so, subjects must initiate oral corticosteroid taper (see Section 5.3.2)
- Document any change to physiotherapy since the previous study visit
- DOW assessment
- Individual CSMs
- CDASI

- 5-D Itch Score
- Timed Up and Go

8.5.3.7 Week 21

The following procedures will be conducted at 20 weeks ± 3 days after the first SC infusion of IMP:

- Body weight
- IMP assignment
- Vital signs
- Safety assessments
- Collection of urine sample for hCG pregnancy test, if applicable
- Collection of blood samples for exploratory biomarkers (serum analysis)
- Collection of blood samples to assess the following:
  - Muscle enzymes
  - Coagulation
  - Serum IgG
- Subject SC Infusion Diary review
- Document AEs
- Document concomitant therapies
- Document any change to physiotherapy since the previous study visit
- DOW assessment
- Assess if subject has clinically relevant improvement, and if so, subjects must initiate oral corticosteroid taper (see Section 5.3.2)
- Individual CSMs
- CDASI

8.5.3.8 Week 25

The following procedures will be conducted at 24 weeks ± 3 days after the first SC infusion of IMP:

- General physical examination
- Body weight
- Waist circumference
- IMP assignment
- Vital signs
- Safety assessments
- Collection of urine sample for hCG pregnancy test, if applicable
- Collection of blood samples for exploratory biomarkers (RNA and serum analyses)
- Collection of blood samples to assess the following:
  - Hematology
  - $HbA1_c$
  - Muscle enzymes
  - Other biochemistry
  - Coagulation
  - Serum IgG
  - ANA, MSA, and MAA
- Subject SC Infusion Diary review
- Document AEs
- Document concomitant therapies
- Document any change to physiotherapy since the previous study visit
- DOW assessment
- Assess if subject has clinically relevant improvement, and if so, subjects must initiate oral corticosteroid taper (see Section 5.3.2)
- Individual CSMs

- CDASI
- 5-D Itch Score
- Timed Up and Go
- EQ-5D-5L, WPAI-GH, TSQM-9

8.5.4 Study Period 2

During Study Period 2, all participating subjects will receive 28 weeks of active treatment with IgPro20 at 0.5 g/kg SC on a weekly basis. Study Period 2 starts with administration of IgPro20 at Week 25, after all Week 25 assessments (as specified in Section 8.5.3.8) have been completed. Study Period 2 continues through the Week 53 Visit when the subject's eligibility for continuation of IgPro20 treatment in Study Period 3 will be confirmed (Section 8.5.4.7). Subjects not eligible for participation in Study Period 3 must complete the Week 56 Safety Follow-up Telephone Call (Section 8.5.4.8).

Study assessments will be performed as specified in the Schedule of Assessments for Study Period 2 (Table 2).

8.5.4.1 Week 29

The following procedures will be conducted at 28 weeks ± 3 days after the first SC infusion of IMP:

- Body weight
- IMP assignment
- Vital signs
- Safety assessments
- Collection of urine sample for hCG pregnancy test, if applicable
- Collection of blood samples to assess the following:
  - Muscle enzymes
  - Coagulation
- Subject SC Infusion Diary review
- Document AEs
- Document concomitant therapies

- Document any change to physiotherapy since the previous study visit
- Assess if subject has clinically relevant improvement, and if so, initiate oral corticosteroid taper
- Individual CSMs
- CDASI

8.5.4.2 Week 33

The following procedures will be conducted at 32 weeks ± 3 days after the first SC infusion of IMP:

- Body weight
- IMP assignment
- Vital signs
- Safety assessments
- Collection of urine sample for hCG pregnancy test, if applicable
- Collection of blood samples to assess the following:
  - Hematology
  - Muscle enzymes
  - Other biochemistry
  - Coagulation
- Subject SC Infusion Diary review
- Document AEs
- Document concomitant therapies
- Document any change to physiotherapy since the previous study visit
- Assess if subject has clinically relevant improvement, and if so, initiate oral corticosteroid taper
- Individual CSMs
- CDASI
- 5-D Itch Score

- Timed Up and Go
- EQ-5D-5L, WPAI-GH, TSQM-9

8.5.4.3 Week 37

The following procedures will be conducted at 36 weeks ± 3 days after the first SC infusion of IMP:

- Body weight
- IMP assignment
- Vital signs
- Safety assessments
- Collection of urine sample for hCG pregnancy test, if applicable
- Collection of blood samples for exploratory biomarkers (serum analysis)
- Collection of blood samples to assess the following:
  - Muscle enzymes
  - Coagulation
  - Serum IgG
- Additional sampling for rich PK analysis, if applicable
- Subject SC Infusion Diary review
- Document AEs
- Document concomitant therapies
- Document any change to physiotherapy since the previous study visit
- Assess if subject has clinically relevant improvement, and if so, initiate oral corticosteroid taper
- Individual CSMs
- CDASI

8.5.4.4 Week 41

The following procedures will be conducted at 40 weeks ± 3 days after the first SC infusion of IMP:

- Body weight
- IMP assignment
- Vital signs
- Safety assessments
- Collection of urine sample for hCG pregnancy test, if applicable
- Collection of blood samples to assess the following:
  - Muscle enzymes
  - Coagulation
- Subject SC Infusion Diary review
- Document AEs
- Document concomitant therapies
- Document any change to physiotherapy since the previous study visit
- Assess if subject has clinically relevant improvement, and if so, initiate oral corticosteroid taper
- Individual CSMs
- CDASI
- 5-D Itch Score
- Timed Up and Go
- EQ-5D-5L, WPAI-GH, TSQM-9

8.5.4.5 Week 45

The following procedures will be conducted at 44 weeks ± 3 days after the first SC infusion of IMP:

- Body weight
- IMP assignment
- Vital signs
- Safety assessments
- Collection of urine sample for hCG pregnancy test, if applicable
- Collection of blood samples to assess the following:
  - Hematology
  - Muscle enzymes
  - Other biochemistry
  - Coagulation
- Subject SC Infusion Diary review
- Document AEs
- Document concomitant therapies
- Document any change to physiotherapy since the previous study visit
- Assess if subject has clinically relevant improvement, and if so, initiate oral corticosteroid taper
- Individual CSMs
- CDASI

8.5.4.6 Week 49

The following procedures will be conducted at 48 weeks ± 3 days after the first SC infusion of IMP:

- Body weight
- IMP assignment
- Vital signs

- Safety assessments
- Collection of urine sample for hCG pregnancy test, if applicable
- Collection of blood samples for exploratory biomarkers (serum analysis)
- Collection of blood samples to assess the following:
  - Muscle enzymes
  - Coagulation
  - Serum IgG
- Subject SC Infusion Diary review
- Document AEs
- Document concomitant therapies
- Document any change to physiotherapy since the previous study visit
- Assess if subject has clinically relevant improvement, and if so, initiate oral corticosteroid taper
- Individual CSMs
- CDASI

8.5.4.7 Week 53

Eligibility for continuation of treatment in Study Period 3 is based on a TIS of ≥ 20 points at Week 49 and is to be confirmed at the Week 53 Visit. If the subject is not eligible to continue treatment with IgPro20, study participation will end with the Week 56 Safety Follow-up Telephone Call (see Section 8.5.4.8). If a subject is withdrawn from the study before the Week 53 Visit, the investigator should make every effort to perform the assessments scheduled for the Week 53 Visit:

- General physical examination
- 12-lead ECG
- Body weight
- Waist circumference
- IMP assignment, if subject is eligible to continue treatment with IgPro20 in Study Period 3

- Vital signs
- Safety assessments
- Collection of urine sample for hCG pregnancy test, if applicable
- Collection of blood samples for virology retention and exploratory biomarkers (RNA and serum analyses)
- Collection of blood samples to assess the following:
  - Hematology
  - $HbA1_c$
  - Muscle enzymes
  - Other biochemistry
  - Coagulation
  - Serum IgG
  - ANA, MSA, and MAA
- Subject SC Infusion Diary review
- Document AEs
- Document concomitant therapies
- Document any change to physiotherapy since the previous study visit
- DOW (only applicable to subjects who discontinue IMP treatment before Week 25)
- Individual CSMs
- CDASI
- 5-D Itch Score
- Timed Up and Go
- EQ-5D-5L, WPAI-GH, TSQM-9

- Document reason for withdrawal, if applicable
- Assess the subject's eligibility for treatment continuation in Study Period 3, if applicable

8.5.4.8 Week 56 (Safety Follow-up Telephone Call)

If a subject is not eligible to continue treatment with IgPro20 in Study Period 3, a telephone call to assess AEs and concomitant therapies will occur 4 weeks after last IMP infusion, after which no further study-related procedures will be performed. In this case, the Safety Follow-up Telephone Call constitutes the EOP2 Visit. The Safety Follow-up Telephone Call will not be performed for subjects who discontinue IMP treatment but remain in the study for at least 1 subsequent study visit 4 weeks after IMP discontinuation, or for subjects who continue treatment with IgPro20 in Study Period 3.

8.5.4.9 Unscheduled Study Visit for Study Period 1 or Study Period 2

The following procedures may be conducted at any Unscheduled Study Visit that occurs during Study Period 1 or Study Period 2:

- Body weight
- IMP assignment, if weight change (> 2 kg) requires dose volume adjustment
- Vital signs
- Safety assessments
- Collection of urine sample for hCG pregnancy test, if applicable
- Collection of blood samples for exploratory biomarkers (serum analysis)
- Collection of blood samples to assess the following:
  - Hematology
  - Muscle enzymes
  - Other biochemistry
  - Coagulation
  - Serum IgG
- Subject SC Infusion Diary review
- Document AEs

- Document concomitant therapies
- Document any change to physiotherapy since the previous study visit
- DOW assessment if before Week 25 (Note: 2 consecutive assessments must be at least 2 weeks apart to meet the criteria for DOW.)
- Assess if subject has clinically relevant improvement, and if so, initiate oral corticosteroid taper
- Individual CSMs
- CDASI
- SC infusion, if applicable, at Week 3 or Week 4 only

8.5.5 Study Period 3

During Study Period 3, subjects will be treated with open-label IgPro20 at 0.5 g/kg SC on a weekly basis and subjects will be asked to return to the study site to complete safety assessments and measurement of body weight on a monthly basis as specified in the Schedule of Assessments for Study Period 3 (Table 3). Additionally, efficacy assessments will be performed at 6-month and 12-month intervals during the subject's continued participation in Study Period 3. Adverse events and concomitant medications will be assessed throughout the subject's participation in the study.

If a subject is withdrawn from the study before completing the EOP3 Visit, all EOP3 Visit assessments should be performed at the last study visit.

8.5.5.1 Monthly (every 4 weeks) Study Visits

The following procedures will be conducted at each monthly study visit (± 7 days) during Study Period 3:

- Body weight
- IMP assignment (weight change of >2kg requires dose volume adjustment)
- Subject SC Infusion Diary review
- Document AEs
- Document concomitant therapies

8.5.5.2 Study Visits Every 6 Months (24 weeks)

In addition to assessments collected at monthly visits, the following will be conducted every 6 months (24 weeks):

- Collection of urine sample for hCG pregnancy test, if applicable
- Vital signs
- Body weight
- Efficacy Assessment (4 Individual CSMs):
  - Physician Global VAS
  - Patient Global VAS
  - MMT-8
  - HAQ
- CDASI
- EQ-5D-5L
- IMP assignment
- IMP SC weekly infusions
- Subject SC infusion diary review

8.5.5.3 End of Year Visit

During participation in Study Period 3, subjects may continue treatment with open-label IgPro20 0.5 g/kg SC weekly until the end of the study (see Section 3.7). At scheduled study visits at the end of each year (± 7 days) during the subject's participation in Study Period 3, the following assessments will be performed in addition to the assessments specified for the study visits every month (see Section 8.5.5.2):

- Collection of urine sample for hCG pregnancy test, if applicable
- General physical examination
- Vital signs
- Collection of blood samples to assess the following:
  - Hematology
  - Biochemistry
- Efficacy Assessment (4 Individual CSMs):
  - Physician Global VAS
  - Patient Global VAS
  - MMT-8
  - HAQ
- CDASI
- EQ-5D-5L
- IMP Assignment for subjects continuing in Study Period 3
- IMP SC weekly infusions for subjects continuing in Study Period 3
- Document reason for withdrawal, if applicable

8.5.5.4 End of Period 3 Visit

If a subject is withdrawn from the study at any time during Study Period 3, the investigator should make every effort to perform the assessments scheduled for the EOP3 Visit:

- Collection of urine sample for hCG pregnancy test, if applicable
- General physical examination
- Vital signs
- Body weight
- Collection of blood samples for virology retention
- Collection of blood samples to assess the following:
  - Hematology
  - Biochemistry
- Subject SC Infusion Diary review
- Document AEs
- Document concomitant therapies
- Efficacy Assessment (4 Individual CSMs):
  - Physician Global VAS
  - Patient Global VAS
  - MMT-8
  - HAQ
- CDASI
- EQ-5D-5L
- Document reason for withdrawal, if applicable

8.5.5.5 Unscheduled Study Visit for Study Period 3

The following procedures may be performed at any Unscheduled Study Visit that occurs during Study Period 3:

- Collection of urine sample for hCG pregnancy test, if applicable
- Vital signs
- Body weight
- IMP assignment, if weight change (> 2 kg) requires dose volume adjustment
- Safety assessments
- Collection of blood samples to assess the following:
  - Hematology
  - Biochemistry
- Subject SC Infusion Diary review
- Document AEs
- Document concomitant therapies
- Efficacy Assessments (4 Individual CSMs):
  - Physician Global VAS
  - Patient Global VAS
  - MMT-8
  - HAQ
- CDASI
- EQ-5D-5L
- Document reason for withdrawal, if applicable

8.5.6 Discontinuation of IMP

Subjects may discontinue IMP at any time at their own request or at the discretion of the investigator. The investigator should record in the eCRF and in the subject's medical records the reason and date of IMP discontinuation.

Subjects who discontinue IMP will be encouraged to remain in the study until Week 25 if discontinuation occurs before Week 25, or until Week 53, if discontinuation occurs after Week 25, in order to collect study assessments.

If the subject discontinues IMP during Study Period 1 or Study Period 2, all Week 53 assessments (see Section 8.5.4.7) will be performed at the study visit where IMP treatment is discontinued, instead of the assessments scheduled for that particular study visit. If subjects discontinue IMP during Study Period 3, subjects will be withdrawn from the study after they have completed the EOP3 Visit assessments.

See the Schedule of Assessments for details on assessments no longer collected after IMP discontinuation if the subject remains in the study.

9 Adverse Events

9.1 Definitions

9.1.1 Adverse Event

As per the ICH Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal, clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

The period of observation for AEs extends from the time the subject gives informed consent until the end of study participation (see Section 9.4 for further details).

Adverse events may include:

Exacerbation (ie, an increase in the frequency or severity) of a pre-existing condition, with the exception of DM

- Illness present before study entry should be recorded in the medical history section of the eCRF and only be reported as an AE if there is an increase in the frequency or severity of the condition during the study

A clinical event occurring after consent but before IMP administration

Intercurrent illnesses with an onset after administration of IMP

Adverse events do not include:

Any worsening of DM including worsening of DM that meets serious criteria (eg, hospitalization)

Events identified at Screening that meet exclusion criteria

Medical or surgical procedures (the condition that leads to the procedure is the AE)

Situations where an untoward medical occurrence has not taken place, eg:

- Planned hospitalizations due to pre-existing conditions, which have not worsened
- Hospitalizations that occur for procedures not due to an AE (eg, cosmetic surgery)
- Hospitalizations for a diagnostic procedure where the hospital stay is less than 24 hours in duration or for normal management procedures (eg, chemotherapy)
- Overdose of IMP or any concomitant therapy that does not result in any adverse signs or symptoms

For laboratory safety parameters, any instances of absolute values being outside the reference range or changes at any study visit after the start of the study that are considered by the investigator as clinically significant must recorded in the eCRF as AEs. In addition, at the investigator's discretion, any changes or trends over time in laboratory parameters can be recorded in the eCRF as AEs if such changes or trends are considered to be clinically relevant, even if the absolute values are within the reference range.

Laboratory findings do not need to be reported as AEs in the following cases:
Laboratory parameters already beyond the reference range at Screening, unless a further increase/decrease can be considered an exacerbation of a pre-existing condition

Abnormal laboratory parameters caused by mechanical or physical influences on the blood sample (eg, in vitro hemolysis) and flagged as such by the laboratory in the laboratory report

Abnormal parameters that are obviously biologically implausible (eg, values that are incompatible with life or outside the measuring range)

An abnormal laboratory value that cannot be confirmed after repeat analysis, preferably in the same laboratory (ie, the previous result could be marked as not valid and should not necessarily be reported as an AE)

9.1.2 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:
Results in death – The event must be the cause of death for the SAE to meet this serious criterion

Is life-threatening – The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe

Requires in-patient hospitalization or prolongation of existing hospitalization – CSLB considers "hospitalization or prolongation of existing hospitalization" for at least 24 hours as the defining criterion for an SAE. Hospital admissions for planned surgery or for normal disease management procedures (eg, chemotherapy) are not considered as defining criteria for SAEs

Results in persistent or significant disability or incapacity

Is a congenital anomaly or birth defect

Is medically significant – A medically significant event is defined as an event that does not necessarily meet any of the SAE criteria, but which is judged by a physician to potentially jeopardize the subject or require medical or surgical intervention to prevent one of the above outcomes listed as an SAE criterion

Adverse events that do not fall into the above categories are defined as non-serious AEs.

9.1.3 Adverse Event of Special Interest

An AESI is an AE of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor is appropriate. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the sponsor to other parties (eg, IDMC, regulators) will be warranted.

In this study, TEEs will be treated as AESIs. The following 3 narrow standardized Medical Dictionary for Regulatory Activities (MedDRA) queries will be utilized for TEE evaluation:

- Embolic and thrombotic events, arterial
- Embolic and thrombotic events, venous
- Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous

9.2 Severity of Adverse Events

The severity of each AE (ie, nonserious and SAEs) is to be assessed by the investigator as follows:

Severity	Definition
Mild	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

9.3 Causality of Adverse Events

The causal relationship of an AE to either IMP or corticosteroid treatment **must always be assessed** by the investigator (Treating Physician). All AEs will be classified as either **related** or **not related** to either IMP or corticosteroid treatment. The AE eCRF will provide the

option to select either IMP or corticosteroid treatment relatedness (see Section 8.1.2.1 for Monitoring for Corticosteroid Treatment).

Adverse events attributable to corticosteroid administration include but are not limited to the following [Oray et al, 2016]:

- Uncontrolled hypertension defined as average systolic blood pressure ≥ 140 mmHg and/or average diastolic blood pressure ≥ 90 mmHg
- Hypokalemia
- Hyperglycemia
- Weight gain ≥ 5%, increase in waist circumference
- Osteopenia or osteoporosis
- Depression, mania, or other relevant psychiatric diagnoses
- Evidence of peptic ulcer disease or erosive gastritis

The degree of certainty with which an AE is attributed to IMP or an alternative cause (eg, corticosteroid treatment, natural history of the underlying disease, other concomitant therapy) will be determined by how well the event can be understood in terms of:

- Known pharmacology of IMP
- Clinically and/or pathophysiologically plausible context
- Reaction of a similar nature previously observed with similar products, or reported in the literature for similar products as being product related (eg, headache, facial flushing, pallor)
- Plausibility supported by the temporal relationship (eg, the event being related by time to administration or termination of treatment with IMP or corticosteroid treatment, drug withdrawal or reproduced on rechallenge)

When there is uncertainty whether an AE is related to IMP or corticosteroid treatment, the AE should be considered related to IMP. If a causality assessment is not provided for an AE (including an SAE), that AE will be considered related to IMP.

9.4 Observation Period for Adverse Events

The observation period for AE and SAE reporting for an individual subject will start at the time of giving written informed consent for participation in the current study and finish at the EOP3 Visit (or last completed study visit).

If the investigator becomes aware of an SAE that has started after the observation period has finished, and there is at least a possible causal relationship with the IMP, the event must be reported to CSLB (see Section 9.6.3).

9.5 Follow-up of Adverse Events

Every effort should be made to follow AEs until resolution or stabilization. Ongoing, non-serious AEs that have not resolved or stabilized will be followed until resolution, stabilization, or the subject is lost to follow-up. Serious adverse events will be followed until the SAE resolves, stabilizes, or the subject is lost to follow-up.

9.6 Adverse Event Reporting

9.6.1 Adverse Events

At each clinical evaluation, the investigator (or delegate) will determine whether any AEs have occurred. All AEs are to be recorded in the eCRF. If known, the medical diagnosis of an AE should be recorded in preference to the listing of individual signs, laboratory findings, and/or symptoms. The investigator must follow up on the course of an AE until resolution or stabilization. If an AE is ongoing after the end of study participation, the AE will continue to be followed up until resolution, stabilization, or the subject is lost to follow-up.

If, during the study period, a subject presents with a preexisting condition that was not noted at the time of study entry, the condition should be retrospectively recorded in the Medical History eCRF.

9.6.2 Adverse Events of Special Interest

Adverse events of special interest should be reported following expedited reporting procedures, as described for SAEs (Section 9.6.3).

9.6.3 Serious Adverse Events

This study will comply with all applicable regulatory requirements and adhere to the full requirements of ICH Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

For SAEs occurring during the study, the investigator (or delegate) will enter all relevant information in the eCRF.

All SAEs that occur during the course of the study, whether or not causally related to IMP, must be entered into the eCRF and must be reported immediately (within 24 hours of the investigator becoming aware of the event) to CSLB. For Japan sites only, the investigator must also inform the head of the medical institution of the SAE and related information in accordance with the Japanese regulatory requirements and ICH GCP.

Adverse events occurring in the period between the time the subject gave written informed consent and the first exposure to IMP, and meeting 1 or more of the seriousness criteria, must be entered into the eCRF in the same manner as other SAEs.

Any SAE that occurs after the end of study participation that is considered to be causally related to IMP must be **reported immediately (ie, within 24 hours of the investigator becoming aware of the event) to CSLB.** Such events are not entered into the eCRF. For Japan sites only, the investigator must also inform the head of the medical institution of the SAE and related information in accordance with the Japanese regulatory requirements and ICH GCP.

The minimum reporting requirements for reporting of SAEs include:

- Subject identification number
- Suspected medicinal product and/or procedure
- Event term
- Reporting source identification
- If the minimum requirements for reporting are fulfilled, the investigator should not wait to receive additional information to fully document the event.
- In addition, the investigator must:

- If required by local regulations, report all SAEs to the relevant Institutional Review Board (IRB)/Independent Ethics Committee (IEC) within the timeframe specified by the IRB/IEC
- If the subject is an active participant in the study:
  - Enter follow-up information in the eCRF until the SAE has resolved, or, in the case of permanent impairment, until stabilized
  - Ensure that the causality assessment for all SAEs is entered in the eCRF
- If the subject is no longer participating in the study, report the follow-up information to CSLB

In cases of death, the investigator should supply CSLB and the IEC/IRB (as applicable) with any additional information as it becomes available (eg, autopsy reports and detailed medical reports).

9.6.4 Other Significant Events

Not applicable.

9.6.5 Overdose

Any IMP overdose that occurs in association with an adverse sign or symptom must be entered into the eCRF as an AE; if the AE meets any seriousness criteria, the event must be reported as an SAE (see Section 9.6.3).

Details of overdose of IMP (defined in Section 5.1.3.3) must be recorded in the subject SC Infusion Diary. Details of overdose of any concomitant therapy must be recorded in the Concomitant Medication eCRF.

9.6.6 Pregnancy and Breastfeeding

A female subject who becomes pregnant while participating in the study must notify the investigator immediately.

If a female subject becomes pregnant, she must discontinue treatment with IMP, but will be encouraged to remain in the study for the remainder of the planned duration in order to collect safety information.

CSLB must be notified via the CSLB Pregnancy Outcome Form as well as completion of the AE/SAE eCRF identifying the pregnancy, within 5 days of the investigator becoming aware of the pregnancy.

Whenever possible, a pregnancy in a subject exposed to IMP should be followed to term so as to assess any potential occurrence of congenital anomalies or birth defects. Any follow-up information, including premature termination and the status of the mother and child after delivery, should be reported by the investigator to CSLB using a Pregnancy Reporting/Outcome Form.

9.7 IRB/IEC Reporting Requirements

The timeframe within which an IRB/IEC must be notified of deaths and investigational product-related unexpected SAEs is stipulated by each IRB/IEC. It is the investigator's (for Japan sites only: the head of the medical institution's and the investigator's) responsibility to comply with the requirements for IRB/IEC notification. CSLB will provide investigators with all details of all SAEs reported to health authorities. For Japan sites, CSLB will follow local regulations and provide the head of the medical institutions and the investigators with all details of all SAEs excluding the known SAEs that originated outside of Japan. For Japan sites, CSLB will list the sponsor's opinions based on the accumulated evaluations for SAEs that originated outside of Japan in the periodic safety update reports.

10 Statistics

10.1 Sample Size Estimation

The study is designed as a superiority study. The sample size calculation is based on the hypothesis that IgPro20 will have a higher responder rate than placebo based on the TIS assessments at Weeks 17, 21, and 25.

A responder is defined as a subject with a TIS ≥ 20 points at Week 25 and at least 1 of the previous scheduled visits (Week 17 or Week 21), who completes 24 weeks of randomized IMP treatment without the use of rescue corticosteroid treatment.

Two recent studies [Aggarwal et al, 2018; Tjarnlund et al, 2018] of subjects with DM or PM reported the responder rates by the IMACS definition of improvement. However, there are currently no data in the literature on the responder rates in the TIS for subjects with DM. For power simulation, it is assumed that 65% of subjects randomized to IgPro20 and 30% of subjects randomized to placebo have a TIS ≥ 20 points at Week 17. Further, it is assumed that for each subject, the response at Week 21 is conditional on the response at Week 17, and the

response at Week 25 is conditional on the response at Week 21. Assumptions used are detailed in Table 15.

Table 15 Assumptions for Power Analysis

Treatment Sequence[A]	Probability of having a TIS ≥ 20 points at Week 17	Probability of having a TIS ≥ 20 points at Week 21	Probability of having a TIS ≥ 20 points at Week 25
A	65%	90%, if TIS ≥ 20 points at Week 17	90%, if TIS ≥ 20 points at Week 21
		20%, if TIS < 20 points at Week 17, or withdraw, or receive rescue corticosteroid treatment before Week 17	20%, if TIS < 20 points at Week 21, or withdraw, or receive rescue corticosteroid treatment before Week 21
B	30%	90%, if TIS ≥ 20 points at Week 17	90%, if TIS ≥ 20 points at Week 21
		10%, if TIS < 20 points at Week 17, or withdraw, or receive rescue corticosteroid treatment before Week 17	10%, if TIS < 20 points at Week 21, or withdraw, or receive rescue corticosteroid treatment before Week 21

TIS = Total Improvement Score.

[A] Treatment sequence A = 0.5 g/kg IgPro20 for 24 weeks followed by 0.5 g/kg IgPro20 for 28 weeks. Treatment sequence B = placebo for 24 weeks followed by 0.5 g/kg IgPro20 for 28 weeks.

Simulation shows a total of 126 subjects (63 subjects per treatment sequence) will be required for a power of 90% in 1-sided Fisher's exact test at a significance level of 0.025. Fisher's exact test is used in the power simulation as a close approximation to the exact logistic regression model in the primary endpoint analysis.

10.2 Definition of Periods and Reference Visits

The TIS calculation will use Baseline assessments throughout Study Period 1 and Study Period 2 and DOW assessment will use Baseline as the reference visit for Study Period 1 and Study Period 2. Definitions of the start and end of periods and reference visits for all other endpoints are presented in Table 16.

Table 16 Study Periods and Reference Visits

Study Period	Weeks	Start of Study Period	Reference Visit of Period	End of Period[A]
1	Week 1 to Week 25	Start date and time of the first IMP infusion	Baseline (before infusion of IMP)	Week 25 (before infusion of IMP)
2	Week 25 to Week 53/Week 56	Start date and time of the first IMP infusion at Week 25	Baseline (before infusion of IMP) Week 25 (before infusion of IMP)	Week 53 (before infusion of IMP) / Week 56 (for subjects not entering SP3)
3	Week 53 to EOP3	Start date and time of the first IMP infusion at Week 53	Week 53 (before infusion of IMP)	EOP3

IMP = investigational medicinal product; EOP3 = End of Study Period 3; SP3 = Study Period 3.

[A] The end of the period is the listed study visit or the last study visit before/at withdrawal.

10.3 Description of Study Analysis Sets

Screened Analysis Set – SCR

The SCR analysis set comprises all subjects who provide written informed consent and who undergo study Screening procedures.

Modified Intent-to-Treat Analysis Set – mITT

The mITT analysis set is as complete and as close as possible to the Intent-to-Treat (ITT) principle. It comprises all subjects in the SCR who are randomized, meet the major inclusion/exclusion criteria and receive any amount of randomized IMP. The documented failure to take any amount of randomized IMP or the lack of any post randomization efficacy data in Study Period 1 [ICH E9, 1998] will lead to the exclusion of the subject from the mITT. Documentation and final assessment will be done in the Blinded Data Review Meeting (BDRM). The mITT analysis set will be based on the treatment sequence to which subjects is randomized.

Modified Intent-to-Treat Analysis Set Extended – mITT-Ex

The mITT-Ex analysis set comprises all subjects in the mITT who complete the first 24 weeks of double-blind treatment (Study Period 1) and receive any amount of the IMP between Week 25 and Week 53 (Study Period 2). The documented failure to take any amount of randomized IMP between Week 25 and Week 53 (Study Period 2) will lead to the

exclusion of the subject from the mITT-Ex. The mITT-Ex analysis will be based on the treatment sequence to which subjects were randomized.

Safety Analysis Set – SAF

The SAF analysis set comprises all subjects who are randomized and receive any amount of randomized IMP. The safety analysis will be based on the actual treatment sequence received.

Per Protocol Analysis Set – PP

The PP analysis set comprises all subjects in the mITT without protocol violations. Protocol violations will be defined in detail in the BDRM before unblinding for the primary data analysis (ie, when all subjects have completed all assessments for Study Period 1 and the data has been cleaned for primary data analysis). The PP analysis will be based on the treatment sequence to which subjects were randomized.

Safety Analysis Set Extended – SAF-Ex

The SAF-Ex analysis set comprises all subjects in the SAF who complete the first 24 weeks of double-blind treatment (Study Period 1) and receive any amount of the IMP between Week 25 and Week 53 (Study Period 2). The SAF-Ex analysis will be based on the actual treatment sequence received.

Safety Analysis Set IgPro20 – SAF-IgPro20

The SAF-IgPro20 analysis set comprises all subjects in the SAF who are randomized to Sequence A, and all subjects in SAF-Ex who are randomized to Sequence B.

Pharmacokinetic Analysis Set – PK

The PK analysis set comprises all subjects, without any protocol violations that may impact PK analysis, who provide rich PK samples for noncompartmental PK parameter estimation. Protocol violations that may impact PK analysis will be defined in detail in the BDRM before database lock.

Safety Analysis Set for Study Period 3 – SAF-P3

The SAF-P3 Analysis Set comprises all subjects in the SAF-Ex who complete the first 52 weeks of treatment in Study Period 1 and Study Period 2 and receive any amount of the IMP after Week 52 (ie, in Study Period 3).

10.4 Statistical Analyses and Methods for Study Period 1 and Study Period 2

A complete description of the statistical analyses and methods will be available in the SAP, which will be finalized before unblinding for the primary data analysis (ie, when all subjects have completed all assessments for Study Period 1 and the data has been cleaned for primary data analysis).

10.4.1 Subject Disposition and Characteristics

10.4.1.1 Subject Disposition

The number of subjects who are screened, randomized, completed the study, discontinued IMP (including the reason), and withdraw consent from the study (including the reason) will be summarized by treatment sequence, period, and total subjects. Screen failure rates will be presented by reason. The reason for discontinuing IMP or withdrawing of consent from the study will be listed by subject.

10.4.1.2 Subject Characteristics

All demographic and Baseline characteristics summaries will be based on the mITT analysis set and the SAF-P3 analysis set for Study Period 3. They will be presented in summary tables by treatment sequence. Continuous data will be summarized by descriptive statistics and categorical data will be summarized by frequency distributions. Age will be described as both a continuous and a discrete variable. By-subject listings will be provided for demographic and Baseline characteristic data.

10.4.2 Efficacy Analyses

10.4.2.1 Study Hypotheses

The study is designed with the objective of testing the null and the alternative hypotheses for the responder rates (see Section 2.1.2) as defined below:

$$H_0: \pi_{IgPro20} \leq \pi_{Pbo} \qquad \textit{vs.} \qquad H_1: \pi_{IgPro20} > \pi_{Pbo},$$

where $\pi_{IgPro20}$ and π_{Pbo} represent the responder rates with IgPro20 and placebo, respectively. Under the null hypothesis, the assumption is that no beneficial effect is afforded by IgPro20 while the alternative hypothesis states that IgPro20 is effective in increasing the responder rate compared to the placebo arm.

10.4.2.2 Primary Estimand

The primary interest is to quantify the treatment effect of IgPro20

- where the potential confounding effect of rescue corticosteroid treatment is excluded
- where the potential confounding of subjects who withdraw from treatment or withdraw from the study before Week 25 and cannot provide sufficient data to demonstrate a benefit of treatment is excluded, and
- in the absence of premature withdrawal from IMP or the study before Week 25 due to the Ukraine war [EMA Biostatistics Working Party, 2022].

The primary estimand in line with the primary interest of the study is described as follows:

- Population: the target patient population defined by eligibility criteria and who received any amount of randomized IMP treatment and have post baseline efficacy results in Study Period 1 (mITT). See Section 10.3 for details.
- Variable: responder status based on TIS assessments at Weeks 17, 21, and 25
- Intercurrent events:
    - withdrawal from randomized IMP treatment or the study, which is not related to the Ukraine war, or receiving rescue corticosteroid treatment before Week 25 is considered treatment failure
    - withdrawal from IMP or the study that is related to the Ukraine war will be addressed using the hypothetical strategy [Meyer et al, 2020; Collins et al, 2020]
- Population-level summary: responder rate by treatment sequence

10.4.2.3 Primary Efficacy Endpoint

The primary endpoint is the responder status in each treatment sequence based on TIS assessments at Weeks 17, 21, and 25. Following the estimand described in Section 10.4.2.2, a responder is defined as a subject with a TIS ≥ 20 points at Week 25 and at least 1 of the previous scheduled visits (Week 17 or Week 21), who completes 24 weeks of randomized IMP treatment without the use of rescue corticosteroid treatment. Therefore, for subjects who do not withdraw from IMP or the study for reasons that are related to the Ukraine war before Week 25, non-responders will include subjects who meet any 1 of the following:

- TIS < 20 points at Week 25
- TIS < 20 points at both Weeks 17 and 21
- Withdraw from treatment or the study or receive rescue corticosteroid treatment before Week 25

To ensure that the treatment effect is not confounded by the intercurrent event of premature withdrawal from IMP or the study due to the Ukraine war, the hypothetical strategy is applied for this intercurrent event to quantify the treatment effect in the absence of the Ukraine war [Meyer et al, 2020; Collins et al, 2020]. For subjects who do withdraw from IMP or the study for reasons which are related to the Ukraine war before Week 25, scheduled TIS assessments after withdrawal are missing. These missing values can be considered missing at random and multiple imputation will be used to derive the hypothetical post-intercurrent event TIS values and the corresponding response variables assuming that the subjects with missing TIS values continue in the same way as similar subjects in the study who did not withdraw prematurely. Multiple imputation is a simulation based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. The completed data sets can then be analyzed using standard methods (see Section 10.4.2.3.1). Note: If no TIS values are available for the subject for any post-randomization visit during Study Period 1, the subject will be excluded from the mITT analysis set (see Section 10.3).

Details of the multiple imputation process for TIS values and derivation of the responder status are provided below:

- The multiple imputation process will be done for subjects who withdraw from IMP or the study for reasons related to the Ukraine war before Week 25 including all subjects who complete Study Period 1 without receiving rescue medication. TIS values in subjects who withdraw from IMP for reasons related to the Ukraine war before Week

25 that are assessed more than 6 weeks after the last IMP administration will be set to missing. Replacement of missing TIS values after discontinuation of IMP or the study (ie, monotone missings) for subjects who withdraw from IMP or the study for reasons related to the Ukraine war before Week 25 will be done using multiple imputations based on monotone regression with the covariates treatment, country, and Baseline MMT-8 (≤ 142 points vs. >142 points) and TIS values from previous visits (50 imputations) by SAS® PROC MI. The seed of the pseudo random number generator to be used to generate the imputations for missing values will be 30071234.

Note: If intermittent values are missing for any of the data included in the multiple imputation analysis the intermittent values will be imputed first using the MCMC option in SAS® PROC MI 50 times to create 50 data sets with only monotone missings. The corresponding data sets will be used as input data sets for replacement of the trailing missing values with SAS® PROC MI using monotone regression, as the preceding step led already to 50 data sets, the number of imputations in this step is to be set to 1.

- In each of the data sets subjects' responses will be derived according to the definition provided above.
- In order to get data sets including all mITT subjects with complete response information, data of the following subjects will be added to each of the 50 data sets
    - Subjects who withdraw from IMP or the study for reasons not related to the Ukraine war before Week 25 or
    - Subjects who receive rescue medication in Study Period 1

  According to the definition above these subjects are all non-responders.

The TIS is a validated assessment for DM and PM [Aggarwal et al, 2017]. It is the sum of all improvement scores (derived from 6 CSMs) associated with the percent change in each CSM as in Table 17. All 6 CSMs have been established and validated as measurement of myositis disease activity for adult DM/PM clinical studies by the IMACS [Rider et al, 2011; Miller et al, 2001].

According to the Web calculator for 2016 ACR/EULAR Criteria the TIS calculation requires at minimum CSM1 (Physician Global Disease Activity), CSM3 (MMT-8) and at least 2 other CSMs. Missing CSMs are considered as not changed (improvement score = 0).

Table 17 Total Improvement Score (TIS) Using Core Set Measures

Core set measures	Level of improvement based on absolute percent change	Improvement score
Physician Global Disease Activity	Worsening to ≤ 5%	0
	> 5% up to ≤ 15%	7.5
	> 15% up to ≤ 25%	15
	> 25% up to ≤ 40%	17.5
	> 40%	20
Patient Global Activity	Worsening to ≤ 5%	0
	> 5% up to ≤ 15%	2.5
	> 15% up to ≤ 25%	5
	> 25% up to ≤ 40%	7.5
	> 40%	10
Manual Muscle Testing-8	Worsening to ≤ 2%	0
	> 2% up to ≤ 10%	10
	> 10% up to ≤ 20%	20
	> 20% up to ≤ 30%	27.5
	> 30%	32.5
Health Assessment Questionnaire	Worsening to ≤ 5%	0
	> 5% up to ≤ 15%	5
	> 15% up to ≤ 25%	7.5
	> 25% up to ≤ 40%	7.5
	> 40%	10
Muscle Enzyme	Worsening to ≤ 5%	0
	> 5% up to ≤ 15%	2.5
	> 15% up to ≤ 25%	5
	> 25% up to ≤ 40%	7.5
	> 40%	7.5
Extramuscular Global Activity	Worsening to ≤ 5%	0
	> 5% up to ≤ 15%	7.5
	> 15% up to ≤ 25%	12.5
	> 25% up to ≤ 40%	15
	> 40%	20
Total Improvement Score in the patient (scale: 0-100)		

10.4.2.3.1 Primary Efficacy Analysis

For each of the 50 data sets resulting from the multiple imputation process described in Section 10.4.2.3 the primary endpoint analysis of responder status will be based on an exact logistic regression model including fixed effects for treatment, region (Japan vs. non-Japan), and Baseline MMT-8 assessment (≤ 142 points vs. > 142 points). (Note: if a subject is erroneously assigned to the wrong baseline randomization stratum [eg, actual Baseline MMT-8 ≤ 142 points, but randomized in the stratum > 142 points] the analysis will be done according to the actual stratum and not according to the stratum used for randomization: This applies to all analyses.) The corresponding results across the data sets are combined for overall inference using SAS® PROC MIANALYZE according to Rubin's rule to give the 1-sided p-value for hypothesis testing, the odds ratio (IgPro20:placebo), and the corresponding 2-sided 95% CI. The primary endpoint analysis will utilize the mITT analysis set. Statistical significance will be assessed using a 1-sided alpha level of 0.025. The responder rate and corresponding 2-sided 95% CI will be estimated by treatment sequence.

The primary endpoint analysis will be repeated on the PP as a supportive analysis.

10.4.2.3.2 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint

Sensitivity analyses of the primary efficacy endpoint will be performed to examine the robustness of the conclusion from the planned primary endpoint analysis to deviations from its underlying modelling assumptions and limitations in the data. Consistency of findings from the primary and sensitivity or supplementary analyses will be investigated and clinical plausibility of findings will be examined.

The following sensitivity analyses will be done based on the imputed TIS data used for the primary efficacy analysis and combined using Rubin's rule. Sensitivity analyses will address the following aspects:

- Regression model: standard logistic regression model will be fitted instead of exact logistic regression model. In case of non-convergence, the model will run without the fixed effects for region and MMT-8 stratification variable.

- Reasons for withdrawal: sensitivity to the assumption that all early dropouts are non-responders will be assessed in this analysis. The responder status of subjects withdrawn from the study before Week 25 will be set to "responder" if:
    - TIS is ≥ 20 points at the last study visit and at least at either of the previous 2 scheduled visits, and
    - reason for withdrawal is not due to lack of efficacy, or IMP related AEs

An additional sensitivity analysis will be done excluding subjects who drop out for reasons related to the Ukraine war using an exact logistic regression model including fixed effects for treatment, region (Japan vs. non-Japan), and Baseline MMT-8 assessment (≤ 142 points vs. > 142 points).

A supplementary analyses will address the following:

- TIS with restrictions: individual CSMs are considered in addition to the TIS in the evaluation of responses at Week 17, Week 21, and Week 25. A subject should meet all of the following 3 criteria to be considered as showing response at each of the 3 study visits: TIS ≥ 20 points; no deterioration > absolute 10% from Baseline in MMT-8; and no deterioration > absolute 20% from Baseline in any other 2 CSMs. This analysis will exclude subjects who drop out for reasons related to the Ukraine war before Week 25 and thus will be based on an exact logistic regression model including fixed effects for treatment, region (Japan vs. non-Japan), and Baseline MMT-8 assessment (≤ 142 points vs. > 142 points).

The analytical approach in the sensitivity or supplementary analyses will be the same as described in Section 10.4.2.3.1, unless otherwise stated. The sensitivity analyses will be based on the mITT and PP.

10.4.2.4 Secondary Efficacy Endpoints

10.4.2.4.1 Key Secondary Estimand

The key secondary interest is to quantify the treatment effect of IgPro20 under the hypothetical situation where no subjects receive rescue corticosteroid treatment or withdraw from treatment or the study before Week 25.

The key secondary estimands in line with the key secondary interest of the study are described as follows for the continuous key secondary endpoints:

- Population: the target patient population defined by eligibility criteria and who received any amount of randomized IMP treatment and have post baseline efficacy results in Study Period 1 (mITT). See Section 10.3 for details.
- Variables: TIS, changes from Baseline in MMT-8, and changes from Baseline in CDASI total activity score at Week 25
- Intercurrent event: when a subject withdraws from randomized IMP treatment or receives rescue corticosteroid treatment before Week 25, data after withdrawal or rescue will be considered missing for the continuous endpoints, even if data are collected in the study
- Population-level summary: mean of the variables by treatment sequence

The key secondary estimand for the binary key secondary endpoint reduction of oral concomitant corticosteroid dose by at least 25% at Week 25 is described as follows:

- Population: the target patient population defined by eligibility criteria and who received any amount of randomized IMP treatment and have post baseline efficacy results in Study Period 1 (mITT). For details see Section 10.3.
- Variables: reduction of oral concomitant corticosteroid dose at Week 25
- Intercurrent events:
  - withdrawal from randomized IMP treatment or the study which is not related to the Ukraine war or receives oral rescue corticosteroid treatment before Week 25, data after withdrawal or oral rescue will be considered no reduction of oral concomitant corticosteroid even if data are collected in the study
  - withdrawal from IMP or the study which are related to the Ukraine war will be addressed using the hypothetical strategy.
- Population-level summary: percentage of subjects who are able to reduce the oral concomitant corticosteroid dose by at least 25% by treatment sequence

10.4.2.4.2 Key Secondary Endpoint

The following key secondary efficacy endpoints are defined as follows:

- TIS at Week 25
- Changes from Baseline in MMT-8 at Week 25
- Changes from Baseline in CDASI total activity score at Week 25
- Reduction of oral concomitant corticosteroid dose at Week 25

10.4.2.4.3 Key Secondary Efficacy Analyses

Each of the following 3 key secondary efficacy endpoints will be analyzed separately using the MMRM model. The terms to be included in the model for each key secondary endpoint are as follows:

- TIS at Week 25: treatment, study visit, the interaction between treatment and study visit, region, and Baseline MMT-8 assessment (≤ 142 points vs. > 142 points), as fixed effects, subjects as a random effect
- Changes from Baseline MMT-8 at Week 25: treatment, study visit, the interaction between treatment and study visit, and region as fixed effects, Baseline MMT-8 as a continuous covariate, subjects as a random effect
- Changes from Baseline CDASI total activity score at Week 25: treatment, study visit, the interaction between treatment and study visit, region, and Baseline MMT-8 assessment (≤ 142 points vs. > 142 points) as fixed effects, Baseline CDASI total activity score as a continuous covariate, subjects as a random effect

Analyses will start with the unstructured covariance matrix; compound symmetry will be adopted in case of convergence difficulties. The differences between treatment sequences, the corresponding 95% CIs, and 1-sided p-values from the models will be provided. Point estimates for the average values in each treatment sequence will be presented along with their standard errors at all visits.

For subjects who receive rescue corticosteroid treatment or who withdraw from treatment or the study, data after the first administration of rescue corticosteroid treatment or withdrawal from randomized IMP treatment will be considered missing and thus not included in the MMRM analysis.

The following sensitivity analyses are planned for the first 3 key secondary endpoints:

- A tipping point analysis as described in Ouyang, 2017 will be performed as a sensitivity analysis. The base case for the tipping point analysis is to include all available data as collected in the MMRM analysis.

- The tipping point analysis will be repeated under the abovementioned hypothetical estimand, ie, where data obtained after rescue corticosteroid treatment or withdrawal from randomized IMP treatment for any reason are excluded from the MMRM analysis.

The analysis of the fourth key secondary endpoint, ie, the proportion of subjects who are able to reduce the oral concomitant corticosteroid dose by at least 25% at Week 25 will be done in analogy to the analysis of the primary endpoint (see Section 10.3).

For subjects who do withdraw from IMP or the study for reasons which are related to the Ukraine war before Week 25, the resulting missing values can be considered missing at random and multiple imputation will be used to derive the hypothetical post-intercurrent event reduction of oral concomitant corticosteroid dose in percent (%reduction). Replacement of trailing missing %reduction values for Week 17 to Week 25 (ie, monotone missings) will be done if the subject received oral corticosteroid medication at baseline using multiple imputations based on monotone regression with the covariates treatment, country, and Baseline MMT-8 (≤ 142 points vs. > 142 points), baseline oral corticosteroid dose and %reduction values from previous weeks starting at Week 17 (50 imputations) by SAS® PROC MI. Note: If the subject did not receive any oral corticosteroid medication at baseline %reduction will be set to 0. The multiple imputation process will correspond to the one for the primary endpoint described in Section 10.4.2.3. A subject is considered a responder regarding this endpoint, if he/she is able to reduce the oral concomitant corticosteroid dose by at least 25% at Week 25, ie if %reduction is ≥ 25.

For each of the 50 data sets resulting from the multiple imputation process the analysis of the 4th key secondary endpoint will be based on an exact logistic regression model including fixed effects for treatment, region (Japan vs. non-Japan), and Baseline MMT-8 assessment (≤ 142 points vs. > 142 points). The corresponding results across the data sets are combined for overall inference using SAS® PROC MIANALYZE according to Rubin's rule.

The 4 key secondary endpoints will be analyzed with an overall 1-sided alpha level of 0.025. The hypotheses associated with the key secondary endpoints will be formally tested and,

therefore, adjusted for multiplicity as described in Section 10.4.2.4.4. The key secondary analyses will be performed based on the mITT and repeated for the PP.

10.4.2.4.4 Multiplicity

Issues related to multiplicity arising from testing the primary endpoint and key secondary endpoints will be addressed using the serial gatekeeping procedure [Dmitrienko et al, 2013] to control the overall family error rate at a 1-sided significance level of 0.025. Two families of null hypotheses are defined with family 1 consisting of the primary endpoint (H_{01}) and family 2 consisting of the 4 key secondary endpoints in the Treatment Phase (H_{02}, H_{03}, H_{04}, and H_{05}). The null hypothesis associated with each of these endpoints is given below:

- H_{01}: Responder rate in IgPro20 0.5 g/kg is ≤ placebo
- H_{02}: Mean TIS in IgPro20 0.5 g/kg is ≤ placebo at Week 25
- H_{03}: Mean change from Baseline in MMT-8 in IgPro20 0.5 g/kg is ≤ placebo at Week 25
- H_{04}: Mean change from Baseline in CDASI total activity score in IgPro20 0.5 g/kg is ≥ placebo at Week 25
- H_{05}: Proportion of subjects who are able to reduce the oral corticosteroid dose by at least 25% in IgPro20 0.5 g/kg ≤ placebo at Week 25

The general process flow of the hypothesis testing is as follows: the null hypothesis associated with the primary endpoint H_{01} will be tested first. If and only if the resulting 1-sided p-value is ≤ 0.025, testing of H_{02}, H_{03}, H_{04}, and H_{05} will be undertaken; otherwise, further hypothesis testing will cease and H_{02} through H_{05} will be retained.

After H_{01} is rejected, the hypothesis tests associated with key secondary endpoints in the Treatment Phase will be performed using the Hommel step-up procedure at a 1-sided significance level of 0.025. The resulting p-values of the second family are ordered from the smallest to the largest, $P_{(1)}$, $P_{(2)}$, $P_{(3)}$, $P_{(4)}$, with the associated ordered null hypotheses $H_{(1)}$, $H_{(2)}$, $H_{(3)}$, and $H_{(4)}$. The Hommel procedure is described below:

- Step 1: start with the largest p-value $P_{(4)}$. If $P_{(4)} \leq 0.025$, reject all null hypotheses in the family, $H_{(1)}$, $H_{(2)}$, $H_{(3)}$, and $H_{(4)}$. Otherwise, fail to reject $H_{(4)}$ and proceed to Step 2.
- Step 2: test the null hypothesis $H_{(3)}$ associated with the p-value $P_{(3)}$. If $P_{(3)} \leq 0.0125$, reject $H_{(1)}$, $H_{(2)}$, and $H_{(3)}$. Otherwise, fail to reject $H_{(3)}$ and proceed to Step 3.

- Step 3: test the null hypothesis $H_{(2)}$ associated with the p-value $P_{(2)}$. If $P_{(2)} \leq 0.00833$ (or $P_{(3)} \leq 0.01667$ and $P_{(2)} \leq 0.0125$), reject $H_{(1)}$ and $H_{(2)}$. Otherwise, fail to reject $H_{(2)}$ and proceed to the last step, Step 4.
- Step 4: test the null hypothesis $H_{(1)}$ associated with the smallest p-value $P_{(1)}$. If $P_{(1)} \leq 0.00625$, or $P_{(1)} \leq 0.00833$ and $P_{(2)} \leq 0.0125$, or $P_{(1)} \leq 0.00833$ and $P_{(3)} \leq 0.01875$, reject the null hypothesis $H_{(1)}$. Otherwise, fail to reject $H_{(1)}$.

10.4.2.4.5 Other Secondary Efficacy Endpoints and Analyses

All other secondary efficacy endpoints will be summarized descriptively by treatment sequence and visit. Raw data and changes from the reference visit will be summarized at all visits as appropriate. Comparison between treatment sequences will be performed using statistical models as described below. No imputation is planned for missing data in secondary endpoints. P-values from the statistical models are intended to be descriptive.

TIS from Week 5 to Week 53: The TIS values between Week 5 and Week 25 will be analyzed in MMRM as described in Section 10.4.2.3. The TIS values between Week 29 and Week 53 will be analyzed in a similar MMRM model with TIS at Week 25 as a covariate. The percentage of subjects achieving TIS ≥ 20, ≥ 40, and ≥ 60 points will be compared between treatment sequences with a logistic regression model. Kaplan-Meier estimates will be presented for time to first achieving TIS ≥ 20, ≥ 40, and ≥ 60 points for both treatment sequences. Time to first achieving TIS ≥ 20, ≥ 40, and ≥ 60 points during study period 1 will be compared between treatment sequences with a Cox regression model.

Individual CSMs except muscle enzyme and CDASI from Baseline to Week 53: The individual CSMs will be analyzed in the same way as MMT-8 and CDASI described in Section 10.4.2.4.3 by period.

DOW from Baseline to Week 53: The percentage of subjects meeting DOW once, twice, or more than twice, and the percentage of subjects meeting DOW and receiving rescue corticosteroid treatment will be compared between treatment sequences with a logistics regression. Kaplan-Meier estimates will be presented for the time to meeting DOW for the first time from baseline to Week 53 for both treatment sequences. In addition, time to meeting DOW for the first time during Study Period 1 will be compared between treatment sequences with a Cox regression model.

Reduction of oral corticosteroid dose from Baseline to Week 53: The percentage of subjects who start oral corticosteroid dose taper before Week 25 by treatment sequence will

be compared between treatment sequences with an exact logistic regression. Additionally, the percentage of subjects who are able to reduce the oral corticosteroid dose by ≥ 25%, ≥ 50%, ≥ 75% by Week 25 or by Week 53 will be compared between treatment sequences with an exact logistic regression.

Use of rescue corticosteroid treatment from Baseline to Week 25: The percentage of subjects receiving rescue corticosteroid treatment will be compared by treatment sequence with an exact logistic regression by visit.

Mobility, Self-care, and Usual Activities domains of EQ-5D-5L from Baseline to Week 53: The number of subjects having at least 1, 2, or > 2 levels up from Baseline at Week 25 and Week 53 will be compared by treatment sequence using the cumulative distribution function. The cumulative distribution function will also be derived to describe the changes in levels from Week 25 by treatment sequence at Week 41 and Week 53.

10.4.2.5 Subgroup Analyses

Internal consistency of observed treatment effect across major subgroups will be investigated as part of exploratory analyses. Subject groups may include but are not limited to, age, gender, region, MMT-8 (≤ 142 points or > 142 points). Further details will be provided in the SAP.

10.4.3 Safety Analyses

All Safety analyses will be performed separately by treatment sequence based on the SAF, SAF-Ex and overall. Adverse events will be coded using MedDRA version 22.0 or higher. TEAEs are defined as AEs reported at or after the start of study treatment. All AEs regardless of when they were reported will be listed.

- An overview summary of TEAEs, including frequency counts and percentages of subjects and the number of events and TEAE rate per time at risk, including the following:
  - Any TEAE
  - TEAEs related to IMP
  - TEAEs related to corticosteroid treatment
  - Temporally associated TEAEs (defined as an AE with an onset between the start of the IMP infusion and up to 72 hours after the end of IMP infusion)

  - Related TEAEs or temporally associated TEAEs to IMP
  - TEAEs leading to permanent discontinuation of IMP
  - TEAEs leading to withdrawal from study
  - TEAEs leading to IMP dose interruptions
  - AESIs
  - AESIs related to the IMP
  - Temporally associated AESIs (defined as a AESI with an onset between the start of the IMP infusion and up to 72 hours after the end of IMP infusion)
  - Serious TEAEs
  - Serious TEAEs related to the IMP
  - Serious TEAEs related to corticosteroid treatment
  - Temporally associated serious TEAEs (defined as a serious TEAE with an onset between the start of the IMP infusion and up to 72 hours after the end of IMP infusion)
  - Fatal serious TEAEs
- TEAEs will be summarized by severity. In addition, the frequency counts and percentage of AEs will be summarized in descending order of total incidence by preferred term (PT) only and by system organ class (SOC) and PT. The following descriptive tables will be generated for TEAEs, including frequency counts and percentages of subjects and the number of events and TEAE rate per time at risk:
  - TEAEs by SOC and PT
  - TEAEs by SOC, PT, and maximum severity
  - Causally related TEAEs by SOC and PT
  - Temporally associated TEAEs by SOC and PT
  - Causally related TEAEs or temporally associated TEAEs by SOC and PT

The following safety parameters will be analyzed descriptively:

- Hemolysis, suspected or confirmed
- Wells' Criteria score for DVT

- Wells' Criteria score for PE
- Laboratory safety parameters
- Vital signs
- Physical examination

10.4.4 Exploratory Analyses

Pain/discomfort and Anxiety/depression domains of EQ-5D-5L, WPAI-GH, TSQM-9, Timed Up and Go, 5-D Itch Score, Muscle Enzyme, concomitant corticosteroid tapering, and ANA, MSA, and MAA will be described similarly to secondary efficacy endpoints as described in Section 10.4.2.4.5. The observed values and changes from reference visits of these endpoints will be summarized by visit, and treatment sequence as appropriate.

10.4.4.1 Pharmacokinetics Analyses

Serum IgG levels will be summarized by visit, treatment sequence, and period.

Rich PK sampling includes a sufficient number of sampling PK time points (from up to 10 Japanese subjects and 30 non-Japanese subjects) during Week 37 to enable a complete concentration-time IgG profile. IgG concentrations from rich PK sampling will be listed and summarized by nominal (planned) time points. Individual concentration-time profiles and mean (± standard deviation) profiles will be plotted using actual time points for individual plots and nominal (planned) time points for mean profiles.

PK parameters C_{max}, C_{trough}, and AUC will be derived using standard noncompartmental analysis using Phoenix WinNonlin, version 6.3 or higher. C_{max} and C_{trough} will be assessed based on the observed values and the method of AUC estimation will be by linear/log trapezoidal rule. Each of C_{max}, C_{trough}, and AUC will be described using individual listings and summary tables based on the PK analysis set.

Additional information on the planned analyses of PK concentration and PK parameters will be provided in the SAP. A separate PK Report will be appended to the clinical study report.

10.4.5 Interim Analysis

No interim analysis for sample size re-estimation, futility stopping, or efficacy stopping is planned.

The primary data analysis (EOP1 analysis) will be done after all subjects have completed all assessments for Study Period 1. At the time of the EOP1 analysis additional AE, efficacy, and pharmacokinetic data of Study Period 2 will be analyzed. Efficacy analysis of the Study Period 2 data will be restricted to all subjects completing or discontinuing prematurely Study Period 2 at the time of data cut-off for the EOP1 analysis; the adverse events analysis will include all subjects treated in any study period at the time of data cut-off for EOP1 analysis; the pharmacokinetic analysis will include all subjects who have completed the Rich PK sampling at Week 37.

Two additional analyses will be done after all subjects have completed all assessments for Study Period 2 (EOP2 analysis) and one after all subjects have completed all assessments for Study Period 3.

10.5 Statistical Analyses and Methods for Study Period 3

All analyses for Study Period 3 will be based on the SAF-P3.

All secondary efficacy endpoints and all exploratory endpoints referring to Study Period 3 will be analyzed descriptively. TEAEs occurring during Study Period 3 will be summarized descriptively including frequency counts and percentages of subjects and the number of events and TEAE rate per time at risk in analogy to Section 10.4.3.

A complete description of the statistical analyses and methods will be available in the SAP.

11 Quality Assurance

The study may be subject to an audit by CSLB, an authorized representatives of CSLB and/or inspections by an authorized health authority (eg, United States Food and Drug Administration [FDA]). Health authorities may request access to all study documentation, including source documents for inspection and copying, in keeping with local regulations. CSLB will notify the investigator of any upcoming audit/inspection.

In the event of an audit, all pertinent study-related documentation must be made available to the auditors. If an audit or inspection occurs, the investigator at each study site will permit the

auditor/inspector direct access to all relevant documents and allocate their time as well as the time of relevant staff to discuss the findings and any relevant issues.

12 Regulatory and Ethics Considerations

12.1 Regulatory Considerations

CSLB or its agents will submit the appropriate documents to the appropriate global regulatory agencies and will await investigational new drug (IND)/clinical trial application (CTA)/clinical trial notification (CTN) approval/notification before study start.

The procedures set out in this clinical study protocol are designed to ensure that CSLB and the investigator abide by the principles of the current ICH GCP guideline on the conduct, evaluation and documentation of this study, as described in ICH Topic E6 (Guideline for GCP). The study will also be carried out according to all applicable international and national regulatory requirements.

12.2 Institutional Review Board/Independent Ethics Committee

The investigator must submit the clinical study protocol and ICFs for review by an authorized and properly constituted (according to local guidelines) IRB/IEC. Written approval must be received from the IRB/IEC before commencement of the study.

For Japan sites only, the head of the study site should submit a written report to the IRB providing the details of all safety-related information reported by CSLB. In addition, the study continuation is to be reapproved by the IRB annually.

12.3 Subject Information and Informed Consent

Informed consent of subjects according to the standards of GCP and the principles in the Declaration of Helsinki must be implemented in this clinical study before protocol-specified procedures are carried out. Written informed consent is not required for assessments or procedures performed according to standard of care (eg, for diagnosis or treatment); results from such assessments may be used in the determination of study eligibility. Information should be given in both oral and written form and should be deemed appropriate by the IRB/IEC. Subjects, their relatives (or if necessary, legally acceptable representatives) must be given ample opportunity to inquire about details of the study.

The subject (or if necessary, legally acceptable representatives) must be provided with a copy of the signed informed consent form.

Should there be any amendments to the clinical study protocol that would directly affect the subject's participation in the study (eg, a change in any procedure), the ICF must be amended to incorporate this modification. Subjects must be informed of the change and they must sign the amended ICF indicating that they re-consent to participate in the study.

12.4 Subject Confidentiality

All subject names and contact details will be kept confidential. Subjects will be identified throughout documentation and evaluation by the number allotted to them during the study. Each subject will be told that all study findings will be handled in the strictest confidence.

The investigator at the study site will be responsible for retaining sufficient information about each subject (eg, name, address, phone number and identity in the study) so that regulatory agencies or CSLB may access this information should the need arise. These records should be retained in a confidential manner as long as legally mandated according to local requirements.

Subject medical records pertaining to the study may be inspected/audited at any time by CSLB employees or their duly authorized representatives, a health authority or the IRB/IEC. All records accessed will be strictly confidential. Consent to participate in the study includes consent to these inspections/audits.

12.5 Indemnity and Compensation

CSLB has secured insurance to cover its obligations under both the Indemnity and the Compensation guidelines for injury to subjects involved in the study.

Other details regarding compensation and the obligations of the investigator/CSLB are provided in the Clinical Trial Research Agreement for the study (see Section 13.1).

13 Administrative Considerations

13.1 Clinical Trial Research Agreement

This study will be conducted under a Clinical Trial Research Agreement between CSLB ("Sponsor") and the institutions representing the investigational study sites ("Authority"). Financial support to the investigational sites will be detailed in the Clinical Trial Research Agreement. The Clinical Trial Research Agreement must be signed before the commencement of the study and will clearly delineate the responsibilities and obligations of investigator and CSLB, and will form the contractual basis under which the clinical study will be conducted. Clinical Trial Research Agreements may be executed by electronic

signature (current provider DocuSign) in compliance with 21 Code of Federal Regulations (CFR) Part 11 and simple or advanced electronic signature according to European Union Regulation No 910/2014 – eIDAS.

13.2 Clinical Study Registration and Results Disclosure

CSLB will provide the relevant clinical study protocol information in public databases before or at commencement of the study. CSLB may also provide study information for inclusion in national registries according to local regulatory requirements.

Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original clinical study protocol registration record.

13.3 Implementation of the Clinical Study Protocol and Amendments

With the exception of medical emergencies, no changes or deviations in the conduct of the signed clinical study protocol will be permitted without documented approval of the CSLB Medical Monitor or designee and the IRB/IEC. In the event of a medical emergency, the investigator at the study site will institute any medical procedures deemed appropriate. However, all such procedures must be promptly reported to the CSLB Medical Monitor and the IRB/IEC.

Modifications to the clinical study protocol that may affect subject safety or the way the study is to be conducted will be documented in a protocol amendment, which must be approved by the IRB/IEC.

Administrative changes to the clinical study protocol, defined as minor corrections and/or clarifications that have no effect on the way the study is to be conducted, will not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information.

13.4 Protocol Deviations

All instances where the requirements of the clinical study protocol are not complied with will be tracked. Corresponding subjects may be withdrawn from the study at the discretion of the investigator and/or CSLB. Clinical study protocol deviations arise when either subjects who have been entered in the study and/or the study sites deviate from the IEC/IRB-approved study protocol.

If a major protocol deviation (ie, a deviation that could have a significant effect on the subject's safety, rights, or welfare and/or on the integrity of the study data) occurs, the investigator must notify CSLB and the appropriate IRB/IEC as soon as possible or as per local requirements.

13.5 Documentation and Record Keeping

13.5.1 Data Collection

The physicians (or delegates) will maintain individual records for each subject. These records should include dates when a subject visited the study site, records of vital signs, medical history, or physical examinations, administration of IMP or concomitant therapy, any AEs experienced, efficacy status (improvement or deterioration) and other notes as appropriate. These records (electronic or paper) constitute source data.

Electronic CRF entries will be considered source data if the eCRF is the site of the original recordings (ie, there is no other written or electronic record of the data).

An eCRF will be provided by CSLB for each subject enrolled into the study. The Treating Physician (or delegate) is responsible for ensuring accurate and proper completion of the eCRF in a timely manner so that it always reflects the latest observations on the subjects enrolled in the study. All entries on the eCRF must be supported by source data unless the eCRF is considered source data. All source data will be kept according to all applicable regulatory requirements. Source data must be completed legibly for each subject enrolled into the study and signed by the investigator (or delegate).

The subject SC Infusion Diary will be completed by the subject at home. At each site visit, the Treating Physician (or delegate) will review entries with the subject before recording them in the eCRF.

An electronic clinical outcomes assessment (eCOA) solution will be used by the subjects and physicians.

The eCOA solution is provided as a means to capture electronic source data in a controlled and consistent way, and to provide access to these source data for Treating Physician and Evaluating Physician. The system also allows the subject's health status to be remotely monitored during the study. The data residing in the eCOA system provider's database are considered the source, and are under the control of the Treating Physician and Evaluating Physician at all times.

The eCOA system provider will transfer a copy of the data across to CSLB's clinical data warehouse at a predefined frequency via a secure data channel for systematic review by the CSL clinical team. The eCOA vendor engaged for this study is responsible for providing a solution that conforms to all pertinent regulations. The solution is not in any way intended as a substitute for normal medical care of the subject. The vendor provides the service of hosting of the eCOA data on behalf of the site, until such a time as the site is in receipt of a certified archive copy of all eCOA data relating to subjects at that site and has confirmed it is readable.

13.5.2 Data Quality Assurance

Data generated throughout the study will be monitored and the eCRFs checked against the subject/source (eCOA, IRT, eCRF, etc) for completeness and accuracy. The Treating Physician/Evaluating Physician (or delegate) must provide direct access to source data documents. CSLB's study monitor (or delegate) will perform this function.

The following data are considered source data with regard to Clinician Reported Outcomes:

- Entries recorded directly on a tablet (eCOA) at site (eg, EULAR/ACR Classification Criteria, Physician Global Damage Assessment, MMT-8, MDAAT, CDASI, Timed Up and Go)
- Entries recorded directly on paper (eg, medical history, IgG treatment history, demographics, physical examination, AEs, body weight, vital signs, urine pregnancy test, efficacy status notes)

The site personnel can request, approve and/or execute a data correction to all aspects of the Clinician Reported Outcomes data pursuant to the applicable processes. Changes will be processed as per the data management procedures/plan created for the database where the information is first stored electronically.

The following data are considered source data with regard to Patient Reported Outcomes:

- Entries recorded by the subject directly on the SC Infusion Diary
- Entries recorded by the subject directly on a tablet (eCOA) at site (eg, Patient Global Activity Assessment, HAQ, 5-D Itch [Pruritus] Score, EQ-5D-5L, WPAI-GH, TSQM-9)

Site personnel can request, approve, and/or execute a correction or deletion of subject metadata (any data point not directly entered in the device by the subject) pursuant to the applicable processes. No other modification of the subjects' directly entered data will be allowed.

It is the expectation that, for all executed and/or requested changes to eCOA data, appropriate supplemental source documentation will be maintained to support said changes and that this documentation can be made available for review upon request.

Following completion of eCRF pages and entry of the data into a database, the data will be checked electronically and manually for consistency and plausibility. Queries will be generated for questionable data and clarification sought from the investigator. When possible, queries will be raised within the appropriate systems. These data queries must be resolved in a timely manner by the investigator (or delegate).

13.5.3 Record Retention

The investigator must follow the principles for record retention outlined in the Clinical Trial Research Agreement. An investigator study file prepared by CSLB (or delegate), containing all applicable documents for use at the study site, will be made available to the investigator before the start of the study. All study documentation and materials maintained in the investigator study file must be kept in conformance with applicable national laws and regulations.

All study documentation and materials maintained in the investigator study file at the study site must be available for inspection by CSLB's study monitor (or delegate) to determine that all required documentation is present and correct.

The study may be audited or inspected by qualified delegates from CSLB or a competent health authority.

Following completion of the study, the investigator is responsible for archiving the investigator's study file, the subject's records and the source data according to applicable regulatory requirements.

13.6 Study and Site Closure

CSLB reserves the right to prematurely discontinue or suspend the study either at a particular site or at all study sites at any time and for any reason. If such action is taken, the CSLB Study Monitor (or delegate) will discuss this with the investigator at each study site at that

time and notify the investigators (for Japan sites only: the heads of the medical institutes by the investigators) in writing. If the study is suspended or terminated for safety reasons, all investigators (for Japan sites only: the heads of the medical institutes as well as the investigators) and the relevant regulatory agencies will be immediately notified of the action as well as the reason for the suspension/termination. The investigator (for Japan sites only: the head of the medical institute) at each study site will advise their IRB/IEC overseeing the study of the suspension/termination.

13.7 Clinical Study Report

Clinical study report(s) will be written after the completion of the study. CSLB or its agent will write the report(s) in consultation with the investigator or, if applicable, a nominated coordinating investigator (or delegate). CSLB requires that the coordinating investigator will sign the clinical study report(s).

Progress reports may be provided to the relevant regulatory bodies in accordance with their requirements.

13.8 Use of Data and Publications

The rights and obligations of investigators and CSLB concerning any formal presentation or publication of data collected as a direct or indirect result of this study will be addressed specifically in the Clinical Trial Research Agreement for the study.

14 References

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15 Appendices

Instructions for assessments included in the Appendices will be provided in a manual for use at the study site.

Appendix 1 Signatures

Signature on Behalf of Sponsor

Study Title: **A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of IgPro20 (Subcutaneous Immunoglobulin, Hizentra®) in Adults with Dermatomyositis (DM) – The RECLAIIM Study**

Protocol Number: **IgPro20_3007**

I have read the Clinical Study Protocol, dated 20 October 2022, titled **A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of IgPro20 (Subcutaneous Immunoglobulin, Hizentra®) in Adults with Dermatomyositis (DM) – The RECLAIIM Study** and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

PPD

Signature of Principal Investigator

Study Title:	**A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of IgPro20 (Subcutaneous Immunoglobulin, Hizentra®) in Adults with Dermatomyositis (DM) – The RECLAIIM Study**
Protocol Number:	**IgPro20_3007** Site Number:

I have read the Clinical Study Protocol, dated 20 October 2022, titled **A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of IgPro20 (Subcutaneous Immunoglobulin, Hizentra®) in Adults with Dermatomyositis (DM) – The RECLAIIM Study.**

By signing this Clinical Study Protocol, I agree to conduct the clinical study, after approval by an Institutional Review Board or Independent Ethics Committee (as appropriate), in accordance with the Clinical Study Protocol, the standards of Good Clinical Practice (as defined by the International Conference on Harmonisation) and applicable regulatory requirements.

Changes to the Clinical Study Protocol will only be implemented after written approval is received from CSL Behring and the Institutional Review Board or Independent Ethics Committee (as appropriate) with the exception of medical emergencies.

I will ensure that study staff fully understand and follow the Clinical Study Protocol.

_____ _____

(Signature) Date (DD MMM YYYY)

_____

(Printed name)

_____

(Title)

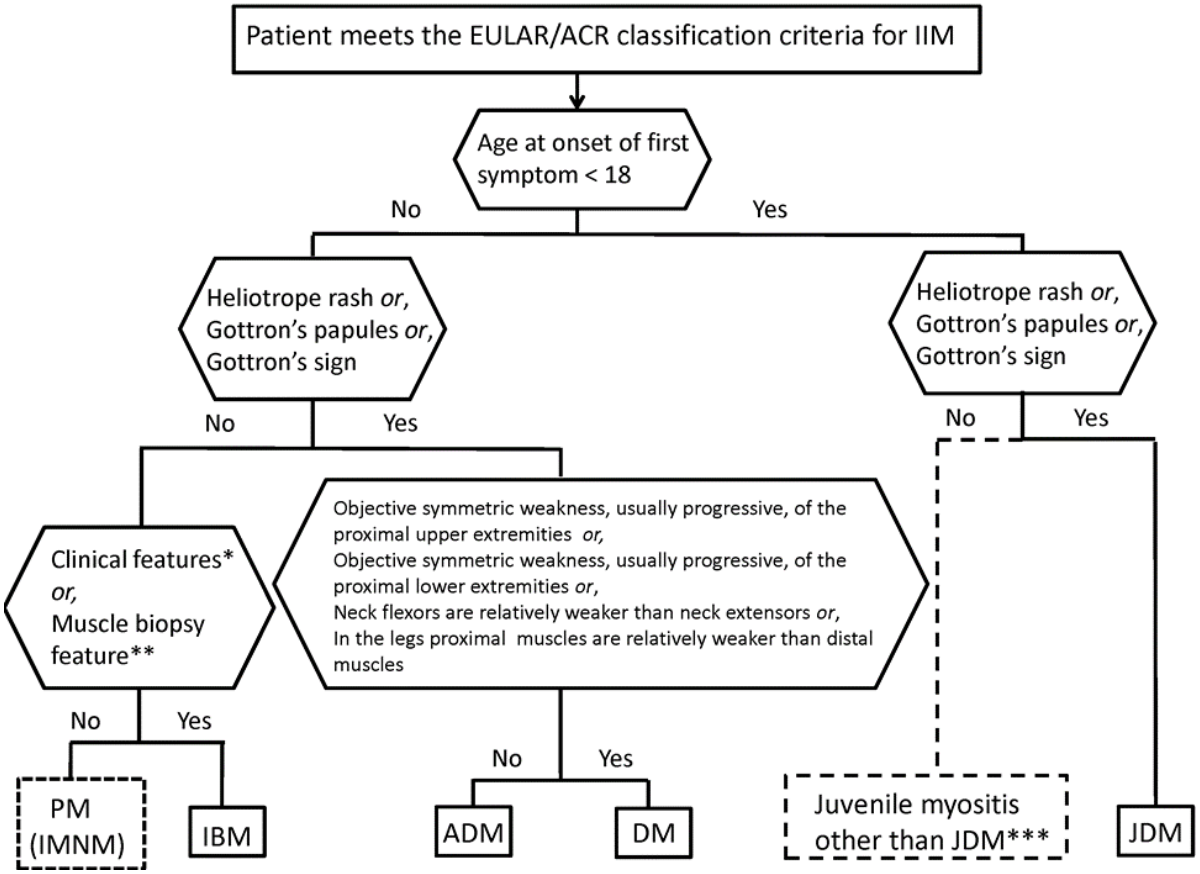
Appendix 2 EULAR/ACR Classification Criteria for Idiopathic Inflammatory Myopathies

When no better explanation for the symptoms and signs exists, these classification criteria can be used

Variable	Score points		
	Without muscle biopsy	With muscle biopsy	Definition
Age of onset			
Age of onset of first symptom assumed to be related to the disease ≥18 years and <40 years	1.3	1.5	18≤Age (years) at onset of first symptom assumed to be related to the disease <40
Age of onset of first symptom assumed to be related to the disease ≥40 years	2.1	2.2	Age (years) at onset of first symptom assumed to be related to the disease ≥40
Muscle weakness			
Objective symmetric weakness, usually progressive, of the proximal upper extremities	0.7	0.7	Weakness of proximal upper extremities as defined by manual muscle testing or other objective strength testing, which is present on both sides and is usually progressive over time
Objective symmetric weakness, usually progressive, of the proximal lower extremities	0.8	0.5	Weakness of proximal lower extremities as defined by manual muscle testing or other objective strength testing, which is present on both sides and is usually progressive over time
Neck flexors are relatively weaker than neck extensors	1.9	1.6	Muscle grades for neck flexors are relatively lower than neck extensors as defined by manual muscle testing or other objective strength testing
In the legs, proximal muscles are relatively weaker than distal muscles	0.9	1.2	Muscle grades for proximal muscles in the legs are relatively lower than distal muscles in the legs as defined by manual muscle testing or other objective strength testing
Skin manifestations			
Heliotrope rash	3.1	3.2	Purple, lilac-coloured or erythematous patches over the eyelids or in a periorbital distribution, often associated with periorbital oedema
Gottron's papules	2.1	2.7	Erythematous to violaceous papules over the extensor surfaces of joints, which are sometimes scaly. May occur over the finger joints, elbows, knees, malleoli and toes
Gottron's sign	3.3	3.7	Erythematous to violaceous macules over the extensor surfaces of joints, which are not palpable
Other clinical manifestations			
Dysphagia or oesophageal dysmotility	0.7	0.6	Difficulty in swallowing or objective evidence of abnormal motility of the oesophagus
Laboratory measurements			
Anti-Jo-1 (anti-histidyl-tRNA synthetase) autoantibody present	3.9	3.8	Autoantibody testing in serum performed with standardised and validated test, showing positive result
Elevated serum levels of creatine kinase (CK)* *or* lactate dehydrogenase (LD)* *or* aspartate aminotransferase (ASAT/AST/SGOT)* *or* alanine aminotransferase (ALAT/ALT/SGPT)*	1.3	1.4	The most abnormal test values during the disease course (highest absolute level of enzyme) above the relevant upper limit of normal
Muscle biopsy features—presence of:			
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibres		1.7	Muscle biopsy reveals endomysial mononuclear cells abutting the sarcolemma of otherwise healthy, non-necrotic muscle fibres, but there is no clear invasion of the muscle fibres
Perimysial and/or perivascular infiltration of mononuclear cells		1.2	Mononuclear cells are located in the perimysium and/or located around blood vessels (in either perimysial or endomysial vessels)
Perifascicular atrophy		1.9	Muscle biopsy reveals several rows of muscle fibres, which are smaller in the perifascicular region than fibres more centrally located
Rimmed vacuoles		3.1	Rimmed vacuoles are bluish by H&E staining and reddish by modified Gomori trichrome stains

*Serum levels above the upper limit of normal.

To be enrolled subject must have a minimum aggregate score of 5.5 without and 6.7 with muscle biopsy



ACR = American College of Rheumatology; ADM = amyopathic dermatomyositis, DM = dermatomyositis; EULAR = European League Against Rheumatism; IBM = inclusion body myositis, IIM = idiopathic inflammatory myopathies; IMNM = immune-mediated necrotizing myopathy; JDM = juvenile dermatomyositis; PM = polymyositis.

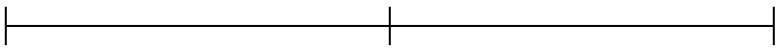
Source: Lundberg et al, 2017.

Appendix 3 Physician Global Damage Assessment

Physician Global Disease Damage Assessment

Disease Damage is defined as persistent changes in anatomy, pathology, physiology, or function, such as fibrosis, scarring, or atrophy, resulting from any cause (including prior treatment) since the onset of the myositis. Features of damage are ascertained by clinical assessment and must be present for at least 6 months (or the pathology that led to the feature must have been present for at least 6 months) despite immunosuppressive or other therapy, including exercise and rehabilitation. The global assessment of disease damage is to be judged from all the information available to you today including the patient's appearance, history, physical examination, diagnostic laboratory testing and your resultant medical therapy.

Please rate your global (overall) assessment of the current myositis disease damage by drawing a vertical mark on the 10-cm. line 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 = extreme or maximum disease.



No evidence of disease damage — Extremely severe disease damage

Also rate global disease damage on a 5-point Likert scale:
___0 = none
___1 = mild damage
___2 = moderate damage
___3 = severe damage
___4 = extremely severe damage

IMACs form 09: Physician Global Damage Assessment

Assessment is only used for eligibility, exclusion criterion # 3

Appendix 4 Myositis Disease Activity Assessment Tool (MDAAT)

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

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

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)**

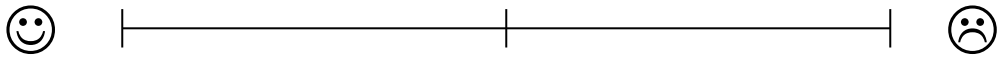
Extramuscular global and global disease activity will be 2 of 6 CSMs used for TIS and DOW calculations

IMACS FORM 7a: Myositis Disease Activity Assessment Tool (MDAAT)

Appendix 5 Patient Global Activity Assessment

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 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, please rate the overall activity of your 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 Global Activity Assessment

Appendix 6 Manual Muscle Testing Scoring Sheet (MMT-8)

Muscle Groups	Right (0 – 10)	Left (0 – 10)	Axial (0 – 10)
Sitting			
Deltoid middle	0-10	0-10	**X**
Biceps brachii	0-10	0-10	**X**
Wrist Extensors	0-10	0-10	**X**
Quadriceps femoris	0-10	0-10	**X**
Ankle dorsiflexors	0-10	0-10	**X**
Supine			
Neck Flexors	**X**	**X**	0-10
Sidelying			
Gluteus medius	0-10	0-10	**X**
Prone			
Gluteus maximus	0-10	0-10	**X**
MMT-8 score (0 – 150)	0-70	0-70	0-10

Muscle groups should be performed in the order listed in table. Muscle groups are tested bilaterally, except neck flexors (axial); **Total MMT-8 score:** 0 – 150 potential range.

IMACS Form 04: Manual Muscle Testing Scoring Sheet
Modified for MMT-8 evaluation, ie, removal of muscle groups associated with MMT26
(score range 0 – 260)

Appendix 7 Health Assessment Questionnaire (HAQ)

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 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 if these activities:

☐ Cane
☐ Devices used for dressing (button hook, zipper pull, shoe horn, etc.)
☐ Walker
☐ Special or built up utensils
☐ Crutches
☐ Special or built up chair
☐ Wheelchair
☐ Other (specify:_____)

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

☐ Dressing and Grooming ☐ Eating

☐ Arising ☐ Walking

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 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 activities:

☐ Raised toilet seat
☐ Bathtub bar
☐ Bathtub seat
☐ Long-handled appliances for reach
☐ Jar opener (for jars previously opened)
☐ Long-handled appliances in bathroom
☐ Other (specify: _____)

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

☐ Hygiene
☐ Gripping and opening things
☐ Reach
☐ 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 <u>VERTICAL</u> (|) MARK ON THE LINE TO INDICATE THE SEVERITY OF PAIN

NO PAIN	**SEVERE PAIN**
0	**100**

IMACS FORM 5a: Health Assessment Questionnaire (HAQ)

Appendix 8 Serum Levels of Muscle Enzymes

Blood Laboratories	Result	Normal Range
Creatine kinase (IU/L)		
Aldolase (IU/L)		
SGOT* (IU/L)		
SGPT* (IU/L)		
LDH (IU/L)		
Creatinine* (mg/dL)		

* Creatinine will not be used for TIS calculation, per Aggarwal 2017, p8.

In addition, the central laboratory will use ALT (SGPT) and AST (SGOT) acronyms for these tests in this study. ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase.

IMACS FORM 06: SERUM LEVELS OF MUSCLE ENZYMES

Appendix 9 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
(For the activity score, please add up the scores of the left side, i.e. Erythema, Scale, Excoriation, Ulceration, Gottron's, Periungual, Alopecia)

Total Damage Score
(For the damage score, add up the scores of the right side, i.e. Poikiloderma, Calcinosis)

Appendix 10 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	☐		

Source: Elman et al, 2010.

Appendix 11 Timed Up and Go

General

- The patient should sit on a standard armchair, placing his/her back against the chair and resting his/her arms chair's arms. Any assistive device used for walking should be nearby.
- Regular footwear and customary walking aids should be used.
- The patient should walk to a line that is 3 meters (9.8 feet) away, turn around at the line, walk back to the chair, and sit down.
- The test ends when the patient's buttocks touch the seat.
- Patients should be instructed to use a comfortable and safe walking speed. A stopwatch should be used to time the test (in seconds).

Set-up

- Measure and mark a 3 meter (9.8 feet) walkway.
- Place a standard height chair (seat height 46 cm, arm height 67 cm) at the beginning of the walkway.

Patient Instructions

- Instruct the patient to sit on the chair and place his/her back against the chair and rest his/her arms chair's arms.
- The upper extremities should not be on the assistive device (if used for walking), but it should be nearby.
- Demonstrate the test to the patient.
- When the patient is ready, say "Go".
- The stopwatch should start when you say go, and should be stopped with the patient's buttocks touch the seat.

Timed Up and Go Testing Form

Name:_____

Assistive Device and/or Bracing Used:_____

Date:_____ TUG Time:_____

Date:_____ TUG Time:_____

Date:_____ TUG Time:_____

Date:_____ TUG Time:_____

Date:_____ TUG Time:_____

Source: Podsiadlo and Richardson, 1991.

Appendix 12 EuroQol 5-Dimension Questionnaire (EQ-5D-5L)

Under Each heading, please tick ONE box that best describes your health TODAY.

Mobility

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

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 (*eg, 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 ❑

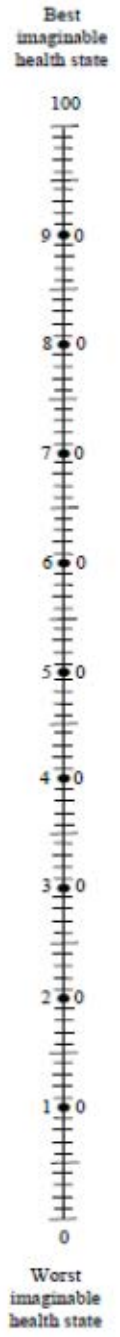
Anxiety/Depression

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	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix 13 Work Productivity and Activity Impairment Questionnaire: General Health v2.0 (WPAI-GH)

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____ NO ____ YES

If NO, check "NO" and skip to question 6.

The next questions are about the **past 7 days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*

_____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

_____HOURS

4. During the past seven days, how many hours did you actually work?

_____HOURS *(If "0", skip to question 6)*

5. During the past seven days, how much did your health problems affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from doing my daily activities

CIRCLE A NUMBER

Source: Reilly et al, 1993.

Appendix 14 Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9)

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical study. We are interested in your evaluation of the effectiveness and convenience of the medication over the last two to three weeks, or since you last used it. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

Extremely Dissatisfied	☐1
Very Dissatisfied	☐2
Dissatisfied	☐3
Somewhat Satisfied	☐4
Satisfied	☐5
Very Satisfied	☐6
Extremely Satisfied	☐7

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

Extremely Dissatisfied	☐1
Very Dissatisfied	☐2
Dissatisfied	☐3
Somewhat Satisfied	☐4
Satisfied	☐5
Very Satisfied	☐6
Extremely Satisfied	☐7

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

Extremely Dissatisfied	☐1
Very Dissatisfied	☐2
Dissatisfied	☐3
Somewhat Satisfied	☐4
Satisfied	☐5
Very Satisfied	☐6
Extremely Satisfied	☐7

4. How easy or difficult is it to use the medication in its current form?

Extremely Difficult	☐1
Very Difficult	☐2
Difficult	☐3
Somewhat Easy	☐4
Easy	☐5
Very Easy	☐6
Extremely Easy	☐7

5. How easy or difficult is it to plan when you will use the medication each time?

Extremely Difficult	☐1
Very Difficult	☐2
Difficult	☐3
Somewhat Easy	☐4
Easy	☐5
Very Easy	☐6
Extremely Easy	☐7

6. How convenient or inconvenient is it to take the medication as instructed?

Extremely Inconvenient	☐1
Very Inconvenient	☐2
Inconvenient	☐3
Somewhat Convenient	☐4
Convenient	☐5
Very Convenient	☐6
Extremely Convenient	☐7

7. Overall, how confident are you that taking this medication is a good thing for you?

Not at All Confident	☐1
A Little Confident	☐2
Somewhat Confident	☐3
Very Confident	☐4
Extremely Confident	☐5

8. How certain are you that the good things about your medication outweigh the bad things?

Not at All Certain	☐1
A Little Certain	☐2
Somewhat Certain	☐3
Very Certain	☐4
Extremely Certain	☐5

9. Taking all things into account, how satisfied or dissatisfied are you with this medication?

Extremely Dissatisfied	☐1
Very Dissatisfied	☐2
Dissatisfied	☐3
Somewhat Satisfied	☐4
Satisfied	☐5
Very Satisfied	☐6
Extremely Satisfied	☐7

Source: Bharmal et al, 2009.

Appendix 15 Weight-based Dosing Regimen

		Number of Weekly Infusion Administrations						
Weight* (kg)	Weekly Volume (mL)	1°	2°	3°	4°	5°	6°	7°
30	75	38	38					
31	77.5	38	38					
32	80	40	40					
33	82.5	42	42					
34	85	42	42					
35	87.5	44	44					
36	90	46	46					
37	92.5	46	46					
38	95	48	48					
39	97.5	48	48					
40	100	50	50					
41	102.5	50	26	26				
42	105	50	28	28				
43	107.5	50	28	28				
44	110	50	30	30				
45	112.5	50	32	32				
46	115	50	32	32				
47	117.5	50	34	34				
48	120	50	36	36				
49	122.5	50	36	36				
50	125	50	38	38				
51	127.5	50	38	38				
52	130	50	40	40				
53	132.5	50	42	42				
54	135	50	42	42				
55	137.5	50	44	44				
56	140	50	46	46				
57	142.5	50	46	46				
58	145	50	48	48				
59	147.5	50	48	48				
60	150	50	50	50				
61	152.5	50	50	26	26			
62	155	50	50	28	28			
63	157.5	50	50	28	28			
64	160	50	50	30	30			

65	162.5	50	50	32	32			
66	165	50	50	32	32			
67	167.5	50	50	34	34			
68	170	50	50	36	36			
69	172.5	50	50	36	36			
70	175	50	50	38	38			
71	177.5	50	50	38	38			
72	180	50	50	40	40			
73	182.5	50	50	42	42			
74	185	50	50	42	42			
75	187.5	50	50	44	44			
76	190	50	50	46	46			
77	192.5	50	50	46	46			
78	195	50	50	48	48			
79	197.5	50	50	48	48			
80	200	50	50	50	50			
81	202.5	50	50	50	26	26		
82	205	50	50	50	28	28		
83	207.5	50	50	50	28	28		
84	210	50	50	50	30	30		
85	212.5	50	50	50	32	32		
86	215	50	50	50	32	32		
87	217.5	50	50	50	34	34		
88	220	50	50	50	36	36		
89	222.5	50	50	50	36	36		
90	225	50	50	50	38	38		
91	227.5	50	50	50	38	38		
92	230	50	50	50	40	40		
93	232.5	50	50	50	42	42		
94	235	50	50	50	42	42		
95	237.5	50	50	50	44	44		
96	240	50	50	50	46	46		
97	242.5	50	50	50	46	46		
98	245	50	50	50	48	48		
99	247.5	50	50	50	48	48		
100	250	50	50	50	50	50		
101	252.5	50	50	50	50	26	26	
102	255	50	50	50	50	28	28	
103	257.5	50	50	50	50	28	28	
104	260	50	50	50	50	30	30	
105	262.5	50	50	50	50	32	32	

106	265	50	50	50	50	32	32	
107	267.5	50	50	50	50	34	34	
108	270	50	50	50	50	36	36	
109	272.5	50	50	50	50	36	36	
110	275	50	50	50	50	38	38	
111	277.5	50	50	50	50	38	38	
112	280	50	50	50	50	40	40	
113	282.5	50	50	50	50	42	42	
114	285	50	50	50	50	42	42	
115	287.5	50	50	50	50	44	44	
116	290	50	50	50	50	46	46	
117	292.5	50	50	50	50	46	46	
118	295	50	50	50	50	48	48	
119	297.5	50	50	50	50	48	48	
120	300	50	50	50	50	50	50	
121	302.5	50	50	50	50	50	26	26
122	305	50	50	50	50	50	28	28
123	307.5	50	50	50	50	50	28	28
124	310	50	50	50	50	50	30	30
125	312.5	50	50	50	50	50	32	32
126	315	50	50	50	50	50	32	32
127	317.5	50	50	50	50	50	34	34
128	320	50	50	50	50	50	36	36
129	322.5	50	50	50	50	50	36	36
130	325	50	50	50	50	50	38	38
131	327.5	50	50	50	50	50	38	38
132	330	50	50	50	50	50	40	40
133	332.5	50	50	50	50	50	42	42
134	335	50	50	50	50	50	42	42
135	337.5	50	50	50	50	50	44	44
136	340	50	50	50	50	50	46	46
137	342.5	50	50	50	50	50	46	46
138	345	50	50	50	50	50	48	48
139	347.5	50	50	50	50	50	48	48
140	350	50	50	50	50	50	50	50

* For weight > 140 kg, please contact CSL Behring to determine the weekly dose volume and appropriate weekly regimen.

Note: Slight adjustment to weekly dose volume (range: -1.5% to 2%) has been made to facilitate the flexible dosing regimens.

Signature Page

IgPro20_3007 - Protocol Amendment - 4 - 20Oct2022

Signed By	Date (GMT)
PPD	28-Oct-2022 06:56:57
Approved-PPD	
PPD	28-Oct-2022 07:09:28
Approved-PPD	
PPD	28-Oct-2022 07:20:07
Approved-PPD	
PPD	28-Oct-2022 07:53:30
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