STATISTICAL ANALYSIS PLAN (SAP)

Study Title:

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

Investigational Medicinal Product: IgPro20 (Hizentra®)

Protocol Number: IgPro20_3007

Version: 5.0

Version Date: 31-JUL-2024

Sponsor:

CSL Behring, LLC

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1 Modification History

Version	Effective Date	Author of Modification	Reason for Change
1.0	see date of last signature	PPD	First Version
2.0	see date of last signature	PPD	**Changes due to Amendment 1 of clinical study protocol dated 07 June 2019** • Modification of study title to include "Pharmacokinetics" • Addition of "Reduction of oral corticosteroid dose at Week 25" as key secondary endpoint; addition of "Reduction of oral corticosteroid dose throughout the study" as a secondary endpoint; addition of "CDASI throughout the study" as a secondary endpoint • Addition of details regarding monitoring for hemolysis with specified criteria (Section 11.6.4) • Clarification for stratification in the case that MMT-8 cannot be fully assessed at Baseline • Addition of detailed description of analysis of Thromboembolic Events (Section 11.3AESI) and Well's criteria (Section 11.6.5) **Changes due to a more detailed explanation of existing analyses** • Addition of derivation for "Corticosteroid Equivalence Dose" (Section 8.2.25) • Addition of derivations for "Study Drug Exposure" (section 8.2.24, replaced section "Actual Volume Infused"; Section 8.2.4) • Addition of derivation for "Study Week" (Section 8.2.3) • Addition of details on the Definition of Worsening (Section 8.2.17)

Version	Effective Date	Author of Modification	Reason for Change
			• Dropping of derivation of %change from baseline, as it is not needed in this study (Section 8.2.6) • Addition of handling of muscle groups which are not assessable for MMT-8 (Section 8.2.12) • Addition of derivation of Abnormality score for Muscle enzymes (Section 8.2.14) • Addition of derivation for "Change of Oral Concomitant Corticosteroid Treatment" (Section 8.2.26) • Dropping of summary for Post Medication as this is considered not necessary (Section 9.4) • Addition of "Non-pharmacological Intervention and Physiotherapy" (Section 9.5) • Addition of subgroup analysis for Disease severity and BMI at baseline (Section 10.2.2) • Addition of the sentence "A virtual timepoint will be added that describes the last individual visit for each subject per period." (Section 10.5, Continuous variables) • Addition of the sentence "The Cox regression will not be done for the whole study duration, as no proportional hazard can be expected." (Section 10.5, Time to event variables) • Addition of sentence "No odds ratios will be calculated for the variables “Subjects meeting DOW at least twice per period” and “Subjects meeting DOW more than twice per period”." (Section 10.5, Response variables) • Addition of more variables as secondary endpoints (Table 11) • Clarification for which safety analysis the periods "Week 1-56" and "IgPro20 Periods" are analyzed (Section 11) • Addition of more details on ”Extent of Exposure" (Section 11.1)

Version	Effective Date	Author of Modification	Reason for Change
			• Deletion of listing "Subject Ids for each serious TEAE" (Section 11.2) **Other Changes** • Minor corrections and clarifications, including word modifications and administrative changes • For ease of reading, Treatment and Visit descriptors are described separately (Section 7.2) • Correction of the description of the Tipping point analysis (Section 10.4.1) • For ease of reading, TIS analysis is described in a separate paragraph (Section 7.2) • Deleting the footnote "Only subjects at risk are included in the analysis, ie, only subjects who received rescue steroid treatment" from Table 11. The subjects at risk are defined for each variable separately.
3.0	see date of last signature	PPD	**Changes due to Amendment 2 (dated 5 February 2020) of clinical study protocol** • Clarification of DOW timing (Section 8.2.17) • Clarification or rescue corticosteroid dose in case of corticosteroid tapering (Section 10.2) **Changes due to Amendment 3 (dated 21 July 2020) of clinical study protocol** • Addition of Study Period 3 to assess the safety and efficacy of long-term treatment with IgPro20 for DM, corresponding endpoints and planned analyses for Study Period 3 • Clarification which analyses are considered sensitivity and which supplementary analyses of the primary endpoint (Section 10.2.1)

Version	Effective Date	Author of Modification	Reason for Change
			• Subgroup analysis for prior use of IgG deleted (Section 10.2.2) • Modified stopping rules and monitoring related to TEEs (Section 11.3) • Minor corrections and clarifications, including word modification **Amendment 4 (dated 15 October 2021) of clinical study protocol** **Note: CSP Amendment 4 (dated 15 October 2021) was signed internally but never implemented.** • Defined that 3 data analyses will be performed, and defined the EOP1 analysis as the primary data analysis • Clarified definitions for reference visits and end of period (Section 8.3) • Corrected minor errors concerning statistical analyses (Hommel procedure Section 4.2.2) • Updated that rate of TEAEs per time at risk will be calculated instead of TEAEs per days with infusion (Section 4.2 and Section 11.2). • Minor corrections and clarifications, including word modification **Other Changes** • Summary measures added for primary and secondary endpoints (Section 4.2) • Specification how Week 53 assessment will be assigned to study visits in case of premature discontinuation of subjects during Study period 1 or 2 (Section 7.2) • Adding analyses to assess the impact of COVID-19 on the study (Section 7.4) • Specification of imputing partial dates for missing concomitant medication end dates (Section 8.1.2)

Version	Effective Date	Author of Modification	Reason for Change
			• Use of derived variables from eCOA for the analysis is restricted to HAQ-DI and CDASI total activity score and total damage score (Section 8.2) • Specification of tapering of corticosteroid treatment (Section 8.2.28) • Specification of the assignment of concomitant medication to Study Period 1, 2 and 3 (Section 8.3.2) • Restrict subgroup analysis for key secondary endpoint to region (Section 10.4.2) • More detailed specification of censoring time (Section 10.5) • Deletion of subgroup analyses for exploratory endpoints (Section 10.6) • Minor corrections and clarifications, including word modification
4	see date of last signature	PPD	**Amendment 4 (dated 20 October 2022) of clinical study protocol** • Update primary and key secondary estimands and statistical methods to account for intercurrent events of withdrawals related to the Ukraine war (Section 10.2, 10.3) • Update mITT definition to exclude subjects who do not meet major inclusion/exclusion criteria or who lack any post randomization efficacy data (Section 6) • Clarified that for the supplementary analysis for TIS with restrictions subjects who drop out for reasons related to the Ukraine war before Week 25 will be excluded. The supplementary analyses referring to rescue corticosteroid treatment were deleted. (Section 10.2.1) • Clarified handling of randomization stratum errors: if a subject is erroneously assigned to the wrong baseline randomization stratum (eg, actual baseline MMT-8≤ 142 points, but randomized in the stratum

Version	Effective Date	Author of Modification	Reason for Change
			> 142 points) the analysis will be done according to the actual stratum and not according to the stratum used for randomization (Section 10.2.2) • Clarified that EOP1 analysis will include pharmacokinetic analysis for all subjects who have completed the rich PK sampling at Week 37 at the time of data cut-off for EOP1 analysis (Section 3, 4.6.1) **Other** • Further specification of tipping point analysis (Section 10.4.1) • Categorical analysis for Timed Up and Go (Section 8.2.29, 10.6) • Simplified the definition of 'end date of last week' (Section 8.2.3) • Added that PK analysis will also be stratified by dosing regimen (Section 12.3)
5	see date of last signature	PPD	• Define time window following IMP discontinuation for efficacy assessments to be included in the analysis if no rescue medication was administered. Previously this time window was to be defined at the BDRM (Section 8.2.3). • Clarification of handling of missing exposure weeks as recorded in the eCRF (Section 8.2.3). • If eCOA assessments at the Baseline/Week 1 visit or the Week 25 visit or the Week 53 visit were assessed after start of IMP administration at the respective visit but within 5 days after start of IMP administration, they will be considered baseline assessments or Week 25 or Week 53 assessments, respectively (Section 8.2.16, 8.3) • Derivation of average daily dose oral corticosteroid dose if length of the respective study week is 0 (Section 8.2.26) • Clarification of tapering algorithm (Section 8.2.28)

Version	Effective Date	Author of Modification	Reason for Change

			• Clarification that multiple imputation will be done for subjects who completed Study Period 1 without the use of oral rescue corticosteroid treatment but have missing TIS values (Section 10.2).
			• Clarification that the imputation model will be changed if inclusion of the variable country is not possible in the imputation model the variables Region (1): Japan, non-Japan and Region (2): USA, non-USA will be included (Section 10.2)
			• Adding additional sensitivity/supplementary analyses for the primary endpoint (Section 10.2.1)
			  • Responder status of withdrawals not due to lack of efficacy or death based on MI
			  • Exclusion of subjects dropping out due to the Ukraine war
			  • Responder status in subjects who have received increased oral corticosteroids without meeting DOW based on TIS results
			  • Threshold for TIS response in primary endpoint increased to 40
			• Adding analysis for secondary endpoints (Section 10.5)
			  • For time to first sustained improvement (exploratory)
			  • For the most abnormal muscle enzyme (CSM 5)
			  • For subjects with available TIS at Week 25 it will be investigated in how many CSMs improvement was achieved.
			  • Proportion of subjects showing an improvement in CDASI Total Activity Score of more than 35% from baseline
			• Adverse event analysis by age group (<65 year, ≥65 years) (Section 11.2)

Version	Effective Date	Author of Modification	Reason for Change
			• Adding the PK parameters clearance and volume of distribution (Section 12.3) • Minor corrections and clarifications, including word modification

2 List of Abbreviations and Glossary of Terms

Abbreviation	Definition
ADaM	Analysis data model
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
BDRM	Blinded data review meeting
BMI	Body mass index
BUN	Blood urea nitrogen
C_{max}	Maximum concentration
C_{trough}	Trough concentration
CDASI	Cutaneous Dermatomyositis Disease Area and Severity Index
CI	Confidence interval
CK	Creatine kinase
CSM	Core set measure
CSR	Clinical study report
DAT	Direct antiglobulin test
HAQ-DI	Health Assessment Questionnaire - Disability index
DM	Dermatomyositis
DOW	Definition of worsening
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCOA	Electronic clinical outcomes assessment
eCRF	Electronic case report form
EOP1	End of Study Period 1
EOP2	End of Study Period 2
EOP3	End of Study Period 3
EQ-5D-5L	EuroQol 5-Dimension 5-Level Questionnaire

Abbreviation	Definition
EULAR/ACR	European League Against Rheumatism / American College of Rheumatology
GGT	Gamma glutamyl transferase
HAQ	Health Assessment Questionnaire
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IDMC	Independent data monitoring committee
IgG	Immunoglobulin G
IMACS	International Myositis Assessment and Clinical Studies Group
IMP	Investigational medicinal product
IRT	Interactive response technology
ITT	Intent-to-Treat
LDH	Lactate dehydrogenase
LS-mean	Least square mean
MAA	Myositis-associated autoantibodies
MAR	Missing at random
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
MSA	Myositis-specific autoantibodies
PE	Pulmonary embolism
PK	Pharmacokinetics
PM	Polymyositis
PP	Per Protocol analysis set
PT	Preferred term
SAE	Serious adverse event
SAF	Safety analysis set
SAF-Ex	Safety analysis set extended

Abbreviation	Definition
SAF-P3	Safety analysis set for Study Period 3
SAP	Statistical analysis plan
SC	Subcutaneous
SCR	Screened Analysis Set
SMQ	Standard MedDRA query
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
UNS	Unscheduled visit
VAS	Visual analog scale
WHO-DDE	World Health Organization - Drug Dictionary Enhanced
WPAI-GH	Work Productivity and Activity Impairment Questionnaire for General Health

Glossary of Terms

Term	Definition
Definition of Worsening (DOW)	The DOW consists of meeting 1 of the following 3 criteria on 2 consecutive study visits at least 2 weeks apart: • Physician Global Activity Assessment Visual Analog Scale (VAS) worsening ≥ 2 cm* and Manual Muscle Test (MMT-8) worsening ≥ absolute 10%, OR • Extramuscular Global Assessment worsening ≥ 2 cm on the Myositis Disease Activity Assessment Tool (MDAAT) VAS, OR • Any 3 of 6 core set measures (CSM) worsening by ≥ absolute 20% * If baseline Physician Global VAS is 8 to10, then any worsening on Physician Global VAS is acceptable as long as MMT-8 criterion is met.
EOP	End of Period distinguishes periods 1, 2 and 3 of the study.

Term	Definition
g/kg	Investigational medicinal product (IMP) dose throughout the study will be calculated by g/kg of body weight. For all dosing references, 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 (see Section 10.2)
Protocol violation	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)
Responder	A subject with a Total Improvement Score (TIS) ≥ 20 points at Week 25 and at least at one of the previous scheduled visits (Week 17 or Week 21), who completes 24 weeks of randomized IMP treatment without the use of oral 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 10.2).
Study treatment	Refers to IMP
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.
Treatment Sequence	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) 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 IgPro20 0.5 g/kg in Study Period 3.
Oral concomitant corticosteroid treatment	Includes both oral rescue and concomitant corticosteroid treatment

3 Purpose

This statistical analysis plan (SAP) provides a detailed and complete description of the planned statistical analyses for the following analyses to be presented in Clinical Study Reports (CSRs):

- primary data analysis of the study IgPro20_3007 including all data collected during Study Period 1 (EOP1 analysis) will be done after all subjects have completed all assessments for Study Period 1
- at the time of the EOP1 analysis additional adverse event, efficacy data, 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. The respective analyses will be based on cleaned data.
- EOP2 analysis will be done after all subjects have completed all assessments for Study Period 2.
- EOP3 analysis will be done after all subjects have completed all assessments for Study Period 3.

Mock tables, listings, and figures shells are provided in separate supporting documents.

This SAP complies with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline Topic E9, Statistical Principles for Clinical Trials. It is based upon the following study documents:

- Study Protocol Amendment 4, (dated 20 October 2022)

All decisions regarding the primary data analysis of the study results, as defined in this SAP document, must be made prior to unblinding of the study data.

4 Study Design

4.1 Study Design

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 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 at Week 53

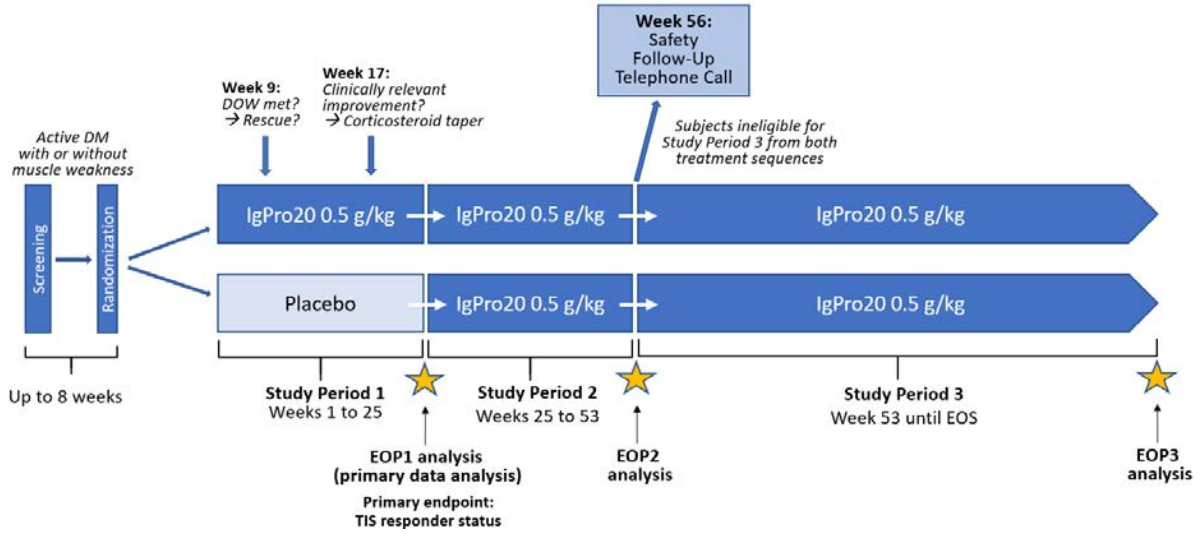
After Screening, subjects will be randomly assigned (1:1) to 1 of 2 sequences of double-blind weekly IMP treatment (0.5 g/kg IgPro20 and placebo). Subjects assigned to **Sequence A** will receive 0.5 g/kg IgPro20 for 24 weeks (Study Period 1) followed by 0.5 g/kg IgPro20 for 28 weeks (Study Period 2). 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, end of Study Period 1 [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 subcutaneous (SC) infusions weekly until the end of the study (see CSP Section 3.7).

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

Figure 1: Study Design



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

4.2 Objectives and Endpoints

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.

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

Table 1: Study Objectives, Endpoints and Summary Measures for Primary and Secondary Endpoints

Objectives	Endpoints	Summary Measure(s)
Primary	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)
Key Secondary		
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
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	• Point estimate 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

Objectives	Endpoints	Summary Measure(s)
Secondary Efficacy		
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
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

Objectives	Endpoints	Summary Measure(s)
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 • Percentage of subjects whose rescue corticosteroid treatment is tapered by treatment sequence • Time to first administration of rescue corticosteroid treatment

Objectives	Endpoints	Summary Measure(s)
1, 3	Mobility, Self-care, and Usual Activities domains of EuroQoL 5-Dimension Questionnaire (EQ-5D-5L) from Baseline to Week 53	• 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 • 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
Secondary Safety		
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

Table 2: Study Objectives and Endpoints for Exploratory Endpoints

Objectives	Endpoints
Exploratory: Study Period 1 and Study Period 2 (From Baseline to Week 53)	
• To assess pain / discomfort and anxiety / depression domains of EQ-5D-5L	• Pain / discomfort and anxiety / depression domains of EQ-5D-5L
• To assess Work Productivity and Activity Impairment Questionnaire for General Health (WPAI-GH)	• WPAI-GH
• To assess Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9)	• TSQM-9
• To assess Timed Up and Go result for functional ability to rise from a chair and ambulate	• Timed Up and Go
• To assess itch (pruritus)	• 5-Dimension (5-D) Itch (pruritus) score
• To assess muscle enzymes	• Creatine kinase (CK) • Lactate dehydrogenase (LDH) • Aspartate aminotransferase (AST) • Alanine aminotransferase (ALT) • Aldolase
• To assess the pharmacokinetics (PK) of IgG in Week 37	• Serum IgG PK parameters
• To assess antinuclear antibodies (ANA) and myositis-specific autoantibodies (MSA) and myositis-associated autoantibodies (MAA)	• ANA, MSA, and MAA
Exploratory: Study Period 3 (After Week 53)	
• To assess the efficacy of IgPro20 from after completion of Week 53 to the end of study participation	• Physician Global Disease Activity, Patient Global Activity Assessment, MMT-8, HAQ-DI, and CDASI from Baseline to EOP3
• To assess quality of life of IgPro20 from after completion of Week 53 to the end of study participation	• Mobility, Self-care, and Usual Activities domains of EuroQol 5-Dimension Questionnaire (EQ-5D-5L) from Baseline to EOP3
• Use of corticosteroid treatment from Week 53 to the end of study participation	• Reduction of average daily dose

4.2.1 Primary Study Hypothesis

The primary study objective is to test the superiority of IgPro20 relative to placebo. The study is designed with the objective of testing the null and the alternative hypotheses for the responder rates as defined below:

$$H_{01}: \pi_{IgPro20} \leq \pi_{Pbo} \quad \text{vs.} \quad H_{11}: \pi_{IgPro20} > \pi_{Pbo}$$

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.

Statistical significance will be assessed using the one-sided alpha level of 0.025.

4.2.2 Key Secondary Endpoints Hypotheses

In addition to the primary study hypotheses, four hypotheses are tested to show the superiority of IgPro20 relative to placebo on key secondary endpoints:

$$H_{02}: {}_{TIS}\mu_{IgPro20} \leq {}_{TIS}\mu_{Pbo} \quad \text{vs.} \quad H_{12}: {}_{TIS}\mu_{IgPro20} > {}_{TIS}\mu_{Pbo}$$

$$H_{03}: {}_{MMT}\mu_{IgPro20} \leq {}_{MMT}\mu_{Pbo} \quad \text{vs.} \quad H_{13}: {}_{MMT}\mu_{IgPro20} > {}_{MMT}\mu_{Pbo}$$

$$H_{04}: {}_{CDASI}\mu_{IgPro20} \geq {}_{CDASI}\mu_{Pbo} \quad \text{vs.} \quad H_{14}: {}_{CDASI}\mu_{IgPro20} < {}_{CDASI}\mu_{Pbo}$$

$$H_{05}: {}_{Cort}\pi_{IgPro20} \leq {}_{Cort}\pi_{Pbo} \quad \text{vs.} \quad H_{15}: {}_{Cort}\pi_{IgPro20} > {}_{Cort}\pi_{Pbo}$$

Where

- ${}_{TIS}\mu_{IgPro20}$ and ${}_{TIS}\mu_{Pbo}$ represent the mean TIS in IgPro20 and placebo at Week 25,
- ${}_{MMT}\mu_{IgPro20}$ and ${}_{MMT}\mu_{Pbo}$ represent the mean change from baseline in MMT-8 in IgPro20 and placebo at Week 25, and
- ${}_{CDASI}\mu_{IgPro20}$ and ${}_{CDASI}\mu_{Pbo}$ represent the mean change from baseline in CDASI total activity score in IgPro20 and placebo at Week 25,
- ${}_{Cort}\pi_{IgPro20}$ and ${}_{Cort}\pi_{Pbo}$ represent the proportion of subjects who are able to reduce the oral concomitant corticosteroid dose by at least 25% in IgPro20 and placebo at Week 25.

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 one-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 (H_{02}, H_{03}, H_{04}, and H_{05}).

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 one-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 will be performed using the Hommel step-up procedure at a one-sided significance level of 0.025. The resulting p-values of the second family are ordered from the smallest to the largest, $P_{(1)}$, $P_{(2)}$, $P_{(3)}$, and $P_{(4)}$ with the associated ordered null hypotheses $H_{(1)}$, $H_{(2)}$, $H_{(3)}$, and $H_{(4)}$. The Hommel step-up 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 $H_{(1)}$.

4.3 Study Treatments

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, eligible subjects may continue treatment with SC infusions of open-label IgPro20 0.5 g/kg.

4.4 Randomization Procedures and Blinding

Eligible subjects will be randomized to 1 of the 2 double-blind treatment sequences by means of Interactive Response Technology (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 CSL Behring 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.

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

The study data will be unblinded for the primary data analysis (ie, end of Study Period 1 [EOP1] analysis) after all subjects have completed all assessments for Study Period 1 and the data has been cleaned for primary data analysis. CSLB site monitors, 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.

4.5 Determination of the Sample Size

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 on 1 of the previous scheduled visits (Week 17 or Week 21) who completes 24 weeks of IMP without the use of oral rescue corticosteroid treatment.

Two recent studies [Aggarwal et al, 2018 and Tjarnlund et al, 2018] of subjects with DM or polymyositis (PM) reported the responder rates by the International Myositis Assessment and Clinical Studies Group (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 3.

Table 3: 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 oral rescue corticosteroid treatment before Week 17	20%, if TIS < 20 points at Week 21, or withdraw, or receive oral 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 oral rescue corticosteroid treatment before Week 17	10%, if TIS < 20 points at Week 21, or withdraw, or receive oral rescue corticosteroid treatment before Week 21

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.

For further details see Appendix 14.1.

4.6 Planned Interim Analyses and Reviews

4.6.1 Interim Analyses Other Than Sample Size Re-estimation

No analysis to stop for futility or other comparisons of treatment arms with respect to efficacy or safety at any time prior to the completion of the study is planned, except as described in Section 4.6.3.

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 adverse event,

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.

4.6.2 Interim Sample Size Re-estimation

Sample size re-estimation is not planned for this study.

4.6.3 Independent Data Monitoring Committee (IDMC) Reviews

The IDMC will monitor the efficacy and safety data generated during the Study Period 1 and 2 in order to conduct unblinded assessments of the benefit-risk profile. Data of Study Period 3 will not be reviewed by the IDMC. The composition, activities, and responsibilities of the IDMC will be described in the IDMC charter. The analyses to support the IDMC data review activities during the study will be detailed in a separate IDMC SAP.

5 Changes in the Conduct of Planned Analyses

There were no changes to analyses planned in the study protocol.

6 Study Analysis Sets

Screened Analysis Set - SCR

The SCR analysis set comprises all subjects who provided 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 were randomized, met the major inclusion/exclusion criteria [ICH E9, 1998] and received any amount of randomized IMP. The

documented failure to take any amount of randomized IMP or the lack of any post randomization efficacy data 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 will be based on the treatment sequence to which subjects were 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.

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 - SAF

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

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 (Week 37) for non-compartmental 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 completed the first 52 weeks of treatment in Study Period 1 and Study Period 2 and received any amount of the IMP after Week 52 (ie, in Study Period 3).

7 General Considerations

Analysis datasets will be created according to CDISC standards and the Study Data Standardization Plan, and data will be displayed according to reporting standards in this SAP.

SAS version 9.3 or higher will be used to perform all data analyses and to generate tables, figures, and listings.

Continuous variables will be summarized in terms of the number of observations, mean, standard deviation, median, Q1, Q3, minimum, and maximum. Other descriptive statistics (eg, coefficient of variation, geometric mean) may be reported when appropriate. Categorical variables will be summarized using frequency counts and percentages. Analyses that use other descriptive statistics will have the specific descriptive statistics required identified with the analysis in the applicable SAP section.

All listings will include subject number, treatment sequence, and randomized treatment of the respective treatment sequence. Unless otherwise stated, all listings will be sorted by treatment sequence, subject number, and then by numeric visit date and time. If any of these variables do not apply to a listing, then that listing will use only those that do in the order given here.

Summary statistics of central tendency will be reported to one more decimal place than the collected data. Summary statistics of variability will be reported to one more decimal place than the commensurate measure of central tendency. For example, the mean and median for age will be reported to one decimal place because it is collected in full years. The standard deviation of age will then be reported to 2 decimal places. Percentages will be displayed to one decimal place.

P-values will be presented with 6 decimal places for primary and key secondary endpoints to ensure proper comparison to significance levels.

Formatting for dates and times will be:

- Dates only – ddmmmyyyy
- Times only – hh:mm or hh:mm:ss (as appropriate)
- Dates and times – ddmmmyyyy hh:mm or ddmmmyyyy hh:mm:ss (as appropriate)

Generally, only pre-specified planned times will be used in the summaries, statistical analyses, and calculations of any derived parameters; unscheduled readings will be included in the listings.

Actual, rather than planned, sampling times will be used in the derivation of PK parameters and in the individual concentration-time plots and listing of PK concentration data. Planned times will be used in the descriptive summaries and in mean plots. Concentration-time data will be listed according to actual sampling times relative to dosing time.

Assessment windows will not be defined for the purpose of classifying measurements obtained outside scheduled assessment times.

Deviations from the analyses in this SAP will be identified in the CSR.

7.1 Multicenter Studies

Pooling of centers will be done for subgroup analysis (see Section 10.2.2). No other pooling of centers will be done.

7.2 Treatment and Visit Descriptors

Period descriptions will show the weeks of interest, eg, Study Period 1 (Week 1 to 25), Study Period 2 (Week 25 to 53) or Study Period 3 (Week 53 to EOP3).

Sequence descriptions will display the respective treatment or treatment sequence.

The line displayed for visit “Baseline” comprises all baseline assessments as defined in Section 8.2.5, which is not necessarily identical to the summary of all assessments from the visit Baseline.

According to the protocol, 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. The Week 53 assessments will be assigned as follows:

- For subjects who discontinue IMP early in Study Period 1 -> EOT P1
- For subjects who discontinue IMP early in Study Period 2 -> EOT P2
- For subjects who do not discontinue IMP early in Study Period 1 or 2 -> Week 53

Analyses by visit will include for the EOT P1 visit the last assessment in Study Period 1 and for EOT P2 the last assessment in Study Period 2.

7.3 Multiple Comparisons and Multiplicity

Issues related to multiplicity are described in Section 4.2.2.

7.4 COVID-19 Impact

During the course of this study, the global COVID-19 pandemic occurred, impacting the study in a variety of ways. This section describes how the impact of COVID-19 will be reported.

Subject Disposition: Study Treatment Discontinuation or Study Discontinuation

Subjects who experience either study treatment discontinuation or study discontinuation due to COVID-19 will have the reason captured in the eCRF. On the appropriate eCRF form to record either study medication discontinuation (“End of Treatment” and / or “End of Treatment Period 3” form) or study discontinuation (“Conclusion of Subject Participation” form), a reason will be selected which includes a field for descriptive text. The reason can be either “Withdrawal by Subject,” “Physician Decision,” or “Other”. The associated free text field entry will include “COVID-19”. When either treatment or the study is discontinued due to an AE or death, the

specific corresponding AE is collected. Discontinuations due to COVID-19 adverse events will then be identified based on whether the MedDRA code for the AE is included in the broad COVID-19 standard MedDRA query (SMQ).

Cases of study treatment discontinuation or study discontinuation due to COVID-19 will be included in the summary of subject disposition.

Demographic and Baseline Characteristics

As only 2 subjects have been enrolled and randomized prior to the COVID-19 pandemic onset, demographic and baseline characteristics will not be summarized by COVID-19 period, ie before and after pandemic onset. COVID-19 pandemic onset will be considered to be 1-Feb-2020.

Subjects with enrollment date after the pandemic onset will be flagged in the listings of demographic and baseline characteristics.

Adverse Events

Adverse events associated with COVID-19, which can include a clinically significant laboratory finding like a positive test result for COVID-19, will be reported by investigators following reporting requirements outlined in the protocol. COVID-19 associated adverse events are identified via MedDRA coding. Relevant adverse events will be identified for reporting by the broad COVID-19 standard MedDRA query (SMQ). All COVID-19 associated adverse events will be included in standard AE tables.

An overview summary table of COVID-19 associated treatment-emergent adverse events (TEAEs), including number and percentages of subjects as well as the number of events, will be provided for the following:

- Any TEAE
- Serious TEAE
- TEAE resulting in death
- TEAE leading to discontinuation of study treatment
- TEAE leading to dose interruptions
- TEAE leading to study withdrawal
- TEAE by maximum severity (mild, moderate, severe, missing)

A listing showing all COVID-19 associated adverse events will be provided.

COVID-19 Vaccinations

Sites will be prompted to inquire whether a subject has received a COVID-19 vaccination and to record each dose of the vaccine on the concomitant medications form along with the exact date of administration and manufacturer of the vaccine. Standardised Drug Grouping (SDG) from WHO Drug Dictionary will be utilized to identify COVID-19 vaccines using the narrow SDG 'Vaccines for COVID-19'. Any vaccination related adverse events experienced by study participants will be recorded on the AE/SAE eCRF page. As a mechanism to assess potential TEAEs associated with the COVID-19 vaccines, those TEAEs occurring within 7 days after COVID-19 vaccine administration will be summarized.

The data will be summarized as described below:

- Summary table by SoC and PT of all TEAEs occurring within 7 days after COVID-19 vaccine administration
- All TEAEs except those occurring within 7 days of COVID-19 vaccination

In addition, the following listings will be provided:

- Listing of all AEs occurring within 7 days after COVID-19 vaccine administration
- Listing of all subjects receiving COVID-19 vaccine

Visit Modality, Missed Visits and Missing Assessments

Changes to subjects' visits caused by the COVID-19 pandemic will be captured for each subject in the eCRF, on the "Visit Status" form. The eCRF page includes different options for the primary visit modality, as well as whether the missed visit/alternate visit modality is due to COVID-19. Since assessments (eg vital signs, laboratory data) collected at each visit are known, the data missing due to COVID-19 can be determined.

Assessments that were missed or required alternate visit modality (eg, televisits or home health visits) due to COVID-19 will be summarized. In addition, number of subjects with missed visits or alternate visit modality, by visit, will be summarized. Data will be listed.

Protocol Deviations

Protocol deviations due to the COVID-19 pandemic will be collected in the Clinical Trial Management System (CTMS) per the study specific Protocol Deviation plan. Pandemic related protocol deviations are identified within CTMS using the sub-category 'COVID-19 Restrictions'.

COVID-19-related protocol deviations will be summarized as sub-categories under existing categories of protocol deviations (see Section 9.2). All COVID-19 related protocol deviations will appear in the listing of protocol deviations and will be flagged.

Overview of COVID-19 Impact

Number and percentages of subjects with at least one of the following due to COVID-19 will be summarized in an overview table:

- Subjects with Any COVID-19 Impact
- Protocol Deviations
- Missing assessment
- Missing Visit
- Alternate Visit Modality
- Study Treatment Discontinuation
- Study Discontinuation
- Any TEAEs
- Any Serious TEAEs

8 Data Handling Conventions

8.1 Missing Data

8.1.1 Imputation of Non-Date Missing Data

Per the protocol, subjects will be encouraged to remain in the study for the remainder of the phase during which they discontinue IMP, in order to collect further study assessments. Missing efficacy data will occur if a subject withdraws consent for additional post-discontinuation assessments. Below is how the missing efficacy data are handled in the key efficacy analyses:

- The primary endpoint analysis considers subjects discontinuing from the study before Week 25 as Non-responders, except for subject who discontinue due to the Ukraine war (see Section 10.2). This consideration is modified in the sensitivity analyses detailed in Section 10.2.1.

- The three continuous key secondary efficacy endpoints are analyzed with MMRM under the Missing at Random (MAR) assumption. No missing data imputation is required for this analysis approach.

- Tipping point analyses will be performed for the key secondary endpoint analyses.

The handling of missing data from questionnaires, CSMs, and other data collection instruments is described in the respective section of the specific instrument.

Subjects with the designation of relationship to IMP and/ or oral corticosteroid treatment for adverse events (AEs) and serious adverse events (SAEs) missing will have the worst case assumed to impute the relationship to IMP:

Relationship as entered in eCRF		**Imputed relationship ***	
to IMP	**to oral corticosteroid treatment**	**to IMP**	**to oral corticosteroid treatment**
missing	missing	*related*	*not related*
related	missing	related	*not related*
not related	missing	not related	*related* **
missing	related	*not related*	related
missing	not related	*related*	not related

* Italic font is used for imputed values

** Only if start of oral corticosteroid treatment was before or at start of AE, otherwise *not related*

There will be no other imputation for missing data other than as described in Section 8.1.2 for partial dates and times.

If the study is terminated early, all available data will be listed, and a review carried out by the study team to assess which statistical analyses are to be performed.

8.1.2 Imputation of Partial Dates

Imputed dates will not be used to derive study day, duration (eg, duration of adverse events), or elapsed time variables.

Partial date imputation will follow Analysis Data Model (ADaM) conventions. The AdaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y'.

blank	indicates that no imputation was done
D = 'Day'	indicates that the day portion of the date is imputed
M = 'Month'	indicates that the month and day portions of the date are imputed
Y = 'Year'	indicates that the entire date (year, month, and day) is imputed

Adverse Events

Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings. They will not be used to calculate duration of AEs. If an AE start or end date is missing, then the duration of the AE will be set to missing.

As a rule, the missing start date elements will be imputed with following priorities:

1. The event is counted as TEAE for IgPro20 with the earliest onset possible.
2. The event is counted as TEAE for Placebo with the earliest onset possible.

In Sequence B, if due to missing elements the event qualifies to either IgPro20 or Placebo, the event is assigned to be treatment-emergent in the IgPro20 period.

If the AE with missing start date elements is related to oral corticosteroid treatment the imputed start date must not be before the start date of the oral corticosteroid treatment.

Date	Missing Element	Rule
Start Date	day, month, and year	Do not impute completely missing AE start dates. <u>Sequence A</u> • The AE will be deemed treatment-emergent in Study Period 1 (Week 1-25) if the AE end date does not indicate that the AE ended prior to IMP start date (week 1), • otherwise the AE will be deemed not treatment-emergent. <u>Sequence B</u> • The AE will be deemed treatment-emergent in Study Period 2 (Week 25-53) if the AE end date does not indicate that the AE ended prior to IMP start date (week 25), • else the AE will be deemed treatment-emergent in Study Period 1 (Week 1-25) if the AE end date does not indicate that the AE ended prior to IMP start date (week 1), • otherwise the AE will be deemed not treatment-emergent.
Start Date	day, month only	<u>Sequence A</u> • If the year of AE start date is the same as the year of IMP start date (week 1), and the AE end date indicates the AE ended after IMP start date (week 1), then set AE start date to IMP start date (week 1), • otherwise set AE month and day to January 1st <u>Sequence B</u> • If the year of AE start date is the same as the year of IMP start date (week 25), and the AE end date indicates the AE ended after IMP start date (week 25), and IMP start date (week 25) is not missing then set AE start date to IMP start date (week 25), • else if the year of AE start date is the same as the year of IMP start date (week 1), and the AE end date indicates the AE ended after IMP start date (week 1) then set AE start date to IMP start date (week 1), • otherwise set AE month and day to January 1st <u>Oral corticosteroid treatment</u> If the AE is related to oral corticosteroid treatment take the later date of first oral corticosteroid treatment start date and the date imputed to the rules in “Sequence A” or “Sequence B” above.
	day only	<u>Sequence A</u> • If the month/year of AE start date is the same as the month/year of IMP start date (week 1), and the AE end date indicates the AE ended after IMP start date (week 1) then set AE start date to IMP start date (week 1),

Date	Missing Element	Rule
		• otherwise set day of AE start date to 1 <u>Sequence B</u> • If the month/year of AE start date is the same as the month/year of IMP start date (week 25), and the AE end date indicates the AE ended after IMP start date (week 25), and IMP start date (week 25) is not missing then set AE start date to IMP start date (week 25), • else if the month/year of AE start date is the same as the month/year of IMP start date (week 1), and the AE end date indicates the AE ended after IMP start date (week 1) then set AE start date to IMP start date (week 1), • otherwise set day of AE start date to 1 <u>Oral corticosteroid treatment</u> If the AE is related to oral corticosteroid treatment take the later date of first oral corticosteroid treatment start date and the date imputed to the rules in "Sequence A" or "Sequence B" above.
End Date	any date element	No imputation for completely or partially missing AE end dates; as applicable, report the AE as ongoing and the AE duration as missing.

Medical History

Date	Missing Element	Rule
Start Date	any date element	No imputation for completely or partially missing start dates
End Date	day, month, and year	Do not impute completely missing Medical History end dates. The Medical History will be deemed "Concomitant medical condition".
	day, month only	Set the end date to December 31st.
	day only	Set the end date to the last day of the month.

Initial Diagnosis of DM

Missing Element	Rule
day, month, and year	No imputation for completely missing dates. Time since first diagnosis will be set to missing.
day, month only	Set the date to January 1st.
day only	Set the date to 1.

Concomitant Medication

Impute start dates for use to derive the reference variables for concomitant medication start relative to treatment; include any imputed dates in analysis datasets with an identifier as imputed. The reference variables will be used to differentiate before, during and after treatment for the concomitant medication.

As a rule, the missing start date elements will be imputed with following priorities:

1. The medication is 'concomitant' to IMP
2. The medication is 'prior' IMP

Date	Missing Element	Rule
Start Date	day, month, and year	Completely missing medication start dates will not be imputed and all values that depend on this date will be set to missing. The medication will be considered 'concomitant'.
	day, month only	• If the year of CM start date is the same as the year of IMP start date (week 1), and the CM end date indicates the CM ended after IMP start date (week 1) then set CM start date to IMP start date (week 1), • otherwise set CM month and day to January 1st
	day only	• If the month/year of CM start date is the same as the month/year of IMP start date (week 1), and the CM end date indicates the CM ended after IMP start date (week 1) then set CM start date to IMP start date (week 1), • otherwise set day of CM start date to 1
End Date	day, month, and year	Medication is considered ongoing at the end of the study.
	day, month only	Set CM end month and day to December 31st
	day only	Set day of CM end date to the last day of the month

8.2 Derived Variables

The following sections provide a general description of the derived and transformed variables to be used in data analyses. Separate analysis dataset specifications provide full details on all data derivations and transformations.

- In this study, an Electronic Clinical Outcomes Assessment (eCOA) device will be used to collect data for several outcomes, and it is used to derive variables for decisions relevant for DOW in Study Period 1.

For the analysis, the eCOA derivations for HAQ-DI and CDASI total activity score and total damage score will be used. All other derivations will be newly programmed.

8.2.1 Reference Dates

Reference dates are used to assign study periods relative to treatment. The reference date is the date of the start of the period (Section 8.3).

8.2.2 Study Day

If the date of interest occurs on or after the date of the start of first IMP infusion then the study day will be calculated as (date of interest – date of the start of first IMP infusion) + 1. If the date of interest occurs before the date of the start of first IMP infusion then the study day will be calculated as (date of interest – date of the start of first IMP infusion). There is no study day 0.

8.2.3 Study Week

The start of a study week is the day of the first infusion of IMP in that week as recorded in the eCRF. For efficacy, the assessments within 7 days following the IMP discontinuation will be included in the analysis if no rescue medication was administered before the respective assessment.

The end of a study week is the day before the start of the next week. In case of missing exposure weeks as recorded in the eCRF planned weeks will be considered as described below.

- End date of the last non-missing week prior to a missing week is 6 days after its start or one day before the start of the next non-missing week (whatever is first).
- End date of the last missing week is 1 day before the start of the next non-missing week.
- In case of multiple consecutively missing weeks, the total gap time is equally distributed across all missing weeks.

In case there is no gap to include a planned missing week between 2 consecutive non-missing weeks the respective week will be flagged in the listings and the length of the planned week will be 0 (see below).

The end of the last week will be defined as follows:

end date of last week = minimum of
(date of EOP, maximum of (date of 1st infusion in last week + 6 days, date of last administration of last week))

For the calculation of average daily dose of oral concomitant corticosteroid treatment, the length of a week will be calculated as

length of week X (days) = maximum of (0, end date of week X – start date of week X + 1)

8.2.4 Time to Event Variables and Durations

The following time to event variables are calculated:

- Time to minimum improvement defined as TIS ≥ 20 points (days)
- Time to moderate improvement defined as TIS ≥ 40 point (days)
- Time to major improvement defined as TIS ≥ 60 point (days)
- Time to meeting DOW for the first time (days)
- Time to first intake of oral rescue corticosteroid treatment
- Time to onset of Adverse Event (days)
- Time since initial diagnosis of DM (months)

The time to event is calculated by period between the date of event minus the date of the respective reference visit (see Section 10.5).

For "Time since initial diagnosis" the length of a month will be assumed to be 30.4375 days:

time since initial diagnosis (months) = (date of screening visit – date of initial diagnosis) / 30.4375

The DOW uses data of two consecutive visits. For the calculation of "Time to meeting DOW" the date of the second of these two visits is used.

Duration of events in days will be calculated as follows:

duration (days) = event end date – event start date + 1

8.2.5 Baseline Definition

Baseline is defined as the most recent, non-missing value prior to or exactly at the start date and time of the first IMP infusion. Results from unscheduled visits will be taken into account.

If date is given for an assessment only, and the date of the assessment is the same as the date of the first IMP infusion then this assessment is NOT considered baseline, except if for the first IMP infusion in Week 1 only the date of IMP administration is documented but the time is missing, assessment documented on that day are considered baseline assessments.

8.2.6 Change from Baseline or Reference Visit

Change from baseline will only be calculated for measures that have post-baseline records. Change from baseline is calculated as:

change from baseline = visit value – baseline value.

If either the baseline or visit value is missing, the change from baseline is set to missing as well.

The change from reference visit will be calculated following the same rules.

8.2.7 Multiple Assessments

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during data set creation). Unscheduled data will only be included in the summary of worst-case analyses of laboratory data, in the analyses of time to improvement and in analyses of DOW.

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

8.2.8 Actual Treatment

The subjects' actual treatment will be derived from exposure data delivered by IRT. If a subject receives IMP that is the same as the assigned treatment, then actual treatment is the assigned treatment. If a subject receives IMP that is different from the assigned treatment for the entire

time of treatment, then actual treatment is the different treatment (the treatment actually received).

8.2.9 Body Mass Index (BMI)

BMI will be calculated using the following formula:

$$\text{BMI (kg/m}^2\text{)} = \text{Weight (kg)} / [\text{Height (m)}]^2$$

using the height measured at Screening and the weight measured at Baseline. If weight at Baseline is not available, the assessment at Screening will be used. If neither is available, then BMI is missing.

8.2.10 CSM1: Physician Global Disease Activity

CSM1 is the Global Disease Activity VAS from MDAAT assessed by the Evaluating Physician (see Figure 9). The potential value range is 0 mm (Absent) to 100 mm (Maximum). Lower values are associated with better state of health. For the TIS, the level of improvement based on absolute percent change ($CSM1_{abs\%}$) must be calculated:

$$CSM1_{abs\%} = ((\text{baseline value} - \text{visit value}) / 100) \times 100$$

8.2.11 CSM2: Patient Global Activity

The subject will assess his/her global DM disease activity at the study visit by selecting a point on a 100 mm line with “No evidence of disease activity” on the left and “Extremely active or severe disease activity” on the right. Lower values are associated with better state of health. For the TIS, the level of improvement based on absolute percent change ($CSM2_{abs\%}$) must be calculated:

$$CSM2_{abs\%} = ((\text{baseline value} - \text{visit value}) / 100) \times 100$$

8.2.12 CSM3: MMT-8

The Evaluating Physician will assess the MMT-8. Eight muscle groups (7 bilateral and 1 axial) are tested in the order of the positions listed in Table 4: Sitting (deltoid middle, biceps brachii,

wrist extensors, quadriceps femoris, ankle dorsiflexors), Supine (neck flexors), Sidelying (gluteus medius), and Prone (gluteus maximus).

CSM3 is the MMT-8 total score. This total score is the sum of all assessments, ranging from 0 up to 150 (exceptions for missing muscle groups see below). Higher scores are associated with increased muscle strength.

Missing scores:

A. Muscle groups that cannot be assessed at baseline will be removed from both the MMT-8 total score and the maximum possible MMT-8 score of the MMT-8 calculation, as well as from the DOW calculation. Even when the muscle group can be assessed later in the study, the absence of a baseline value will justify excluding it from MMT-8 calculations.

B. Some muscle groups assessed at baseline may become impossible to assess later in the study. The MMT-8 calculation will not include the absent muscle group in the MMT-8 total score and the maximum possible MMT-8 score. TIS will be calculated at every visit from the time of the event to the end of the study using a Baseline MMT-8 score that excludes the affected muscle group.

Note: Once a muscle group has not been assessed, the values for all subsequent visits and all preceding visits in the respective study period will be set to missing before any calculation. They are considered as not assessed. These values will be flagged in listings but not used in any derivation.

For the calculation of MMT-8 total score, change from reference visit, and absolute percent change, three different derivations are performed depending on the availability of a muscle group at the last visit of Study Period 1 (Week 1-25), Study Period 2 (Week 25-53), or Study Period 3 (Week 53-EOP3) respectively.

MMT-8 total score with correction at Week 25 (MMT-8_{25})

The MMT-8_{25} total score sums all muscle group that are assessed at Week 25 or end of treatment (if end of treatment is before Week 25).

It will be used for

- primary endpoint analysis
- key secondary endpoint analysis of TIS and Change from Baseline MMT-8, and
- all other analysis of TIS and MMT-8 using only visits up to and including Week 25.

MMT-8 total score with correction at Week 53 ($MMT\text{-}8_{53}$)

The $MMT\text{-}8_{53}$ total score sums all muscle group that are assessed at Week 53 or end of treatment (if end of treatment is before Week 53).

It will be used for all analysis of TIS and MMT-8 which uses visits after Week 25 and up to Week 53.

MMT-8 total score with correction at EOP3 ($MMT\text{-}8_{EOP3}$)

The $MMT\text{-}8_{EOP3}$ total score sums all muscle group that are assessed at EOP3 (or end of treatment during Study Period 3).

It will be used for all analyses of MMT-8 which uses visits after Week 53.

For the TIS, the level of improvement based on absolute percent change ($CSM3_{abs\%}$) must be calculated:

$$CSM3_{abs\%} = 100 \times (\text{visit value} - \text{baseline value}) / (10 \times m)$$

where

- m is the number of muscle groups assessed during the complete periods, with a maximum value of 15,
- the visit value and the baseline are the $MMT\text{-}8_{25}$ or $MMT\text{-}8_{53}$ total scores.

Table 4: 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

8.2.13 CSM4: HAQ

The subject will answer a series of questions which assess how DM is affecting 8 components of daily living: dressing / grooming, arising (position changes), eating, walking, hygiene, reach, grip, and activities, eg, running errands, chores (see Figure 2).

CSM4 is the HAQ-DI score which is delivered by eCOA. The potential values range from 0 to 3. Lower values are associated with better state of health. For the TIS, the level of improvement based on absolute percent change ($CSM4_{abs\%}$) must be calculated:

$$CSM4_{abs\%} = ((\text{baseline value} - \text{visit value}) / 3) \times 100$$

Figure 2: 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 VERTICAL (|) MARK ON THE LINE TO INDICATE THE SEVERITY OF PAIN

NO PAIN **SEVERE PAIN**

0 **100**

8.2.14 CSM5: Muscle Enzymes

The most abnormal muscle enzyme (CK, LDH, AST, ALT, or aldolase) at baseline will be identified by the central laboratory and used for calculating changes during the study [Aggarwal et al., 2017]. If a baseline muscle enzyme is missing, the screening value will be used. The most abnormal muscle enzyme will be determined by considering the value in relation to the outer bounds of the normal range.

$$\text{abnormality score} = \text{baseline value} / \text{ULN}$$

If more than one muscle enzyme has the same abnormality score at baseline, the muscle enzyme is chosen by the following priority order: 1 - CK, 2 - LDH, 3 - AST, 4 - ALT, 5 - aldolase. These rules are consistent with Web calculator for 2016 ACR/EULAR Criteria.

The formula for the absolute percent change uses multiples of Upper Limit of Normal (ULN). The multiple for CK is 15, the multiple for aldolase is 6, and the multiple for ALT, AST, and LDH is 3.

$$CSM5_{abs\%} = ((\text{baseline value} - \text{visit value}) / (\text{multiple} \times \text{ULN})) \times 100$$

8.2.15 CSM6: Extramuscular Global Activity

CSM6 is the Extramuscular Global Assessment VAS from MDAAT (see Figure 9). The potential value range is 0 mm (Absent) to 100 mm (Maximum). Lower values are associated with better state of health. For the TIS, the level of improvement based on absolute percent change ($CSM6_{abs\%}$) must be calculated:

$$CSM6_{abs\%} = ((\text{baseline value} - \text{visit value}) / 100) \times 100$$

8.2.16 TIS

The TIS is a validated assessment for DM and PM. It is the sum of all available improvement scores (derived from the 6 CSMs) associated with the percent change in each CSM as in Table 5.

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).

The TIS calculation will use baseline assessments throughout the study.

CSMs are combined to TIS using the nominal visits. Date of TIS (and possible improvement) is the date of the earliest CSM contributing to the TIS. If some of the core set measures assessed at the Baseline/Week 1 or the Week 25 visit or the Week 53 visit were assessed after start of IMP at the respective visit but within 5 days after start, the core set measures will be considered baseline assessments or included in the TIS calculation for Week 25 or for Week 53, respectively. All these cases will be presented during the BDRM. The same approach will be applied for all other data collected in eCOA data.

Table 5: TIS Using CSMs

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
MMT-8	Worsening to ≤ 2%	0
	> 2% up to ≤ 10%	10
	> 10% up to ≤ 20%	20
	> 20% up to ≤ 30%	27.5
	> 30%	32.5
HAQ	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

Core set measures	Level of improvement based on absolute percent change*	Improvement score
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)		

* For calculation of absolute percent change see section describing the resp. CSMs

8.2.17 DOW

A subject who meets at least 1 of the following 3 criteria on 2 consecutive study visits at least 2 weeks apart, as compared to reference visit will be considered to have met the DOW.

- Physician Global Disease Activity Assessment VAS (CSM 1) worsening ≥ 2 cm* and MMT-8 worsening (CSM 3) ≥ absolute 10%, or
- Extramuscular Global Assessment VAS worsening (CSM 6) ≥ 2 cm, or
- Any 3 of 6 CSM worsening by ≥ absolute 20%.

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

The reference visit for DOW is the baseline visit.

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.

8.2.18 5-D Itch (Pruritus) Score

Subjects will assess 5 dimensions of itch history: Duration, Degree (intensity), Direction (better or worse from previous month), Disability of 4 activities of daily living, and Distribution (location[s] on body). Calculation of the score is described in Elman et al, 2010.

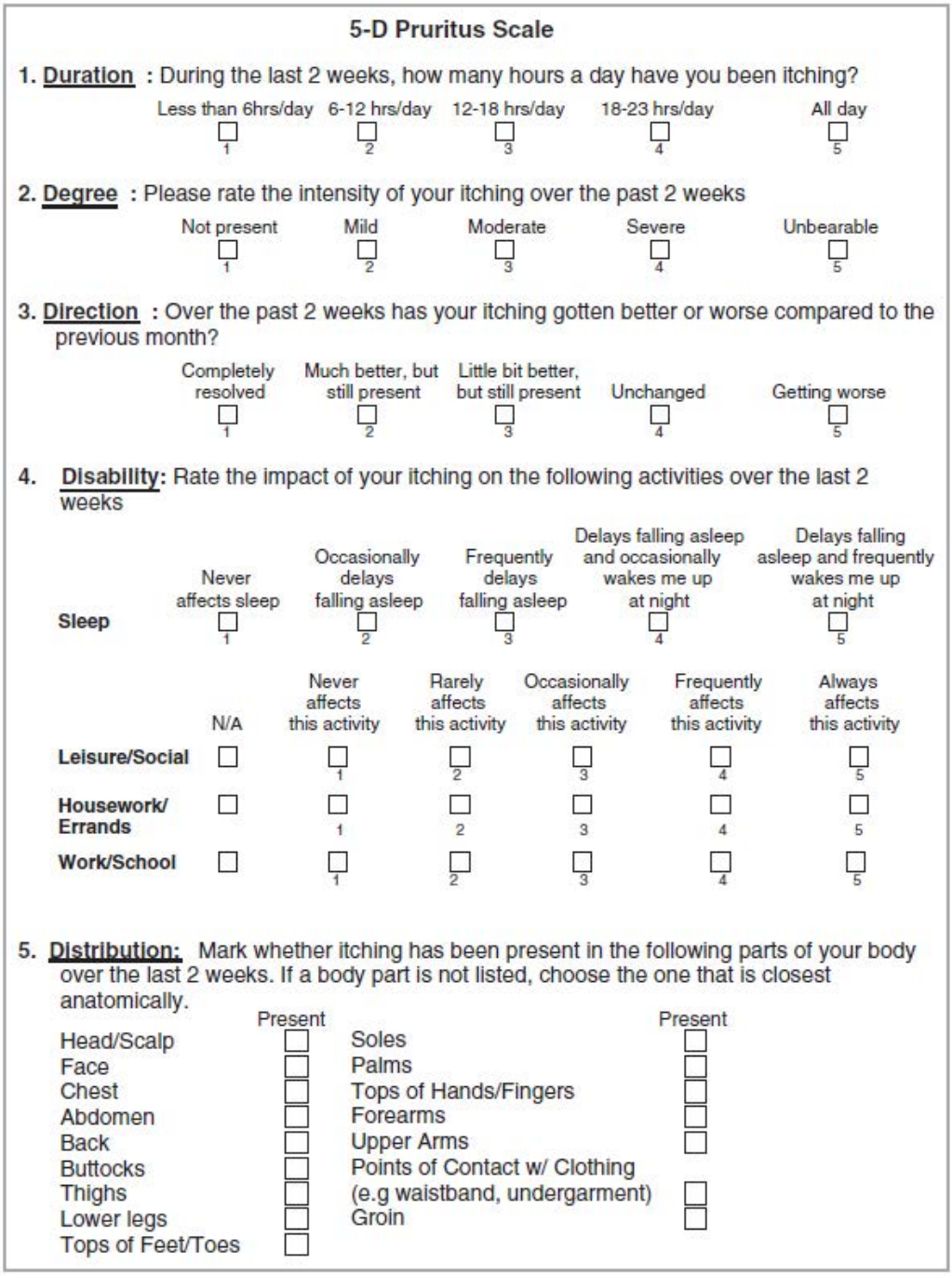
The scores of each of the five domains are achieved separately and then summed together to obtain a total 5-D score. 5-D scores range between 5 (no pruritus) and 25 (most severe pruritus).

- Single-item domain scores (**duration**, **degree** and **direction**) are equal to the value indicated below the response choice (range 1–5). If one or more of these domain scores are missing the total score will be missing.

- The **disability** domain includes four items that assess the impact of itching on daily activities: sleep, leisure/social activities, housework/errands and work/school. The score for the disability domain is achieved by taking the highest score on any of the four items. If all disability items are missing or N/A the total score will be missing.

- For the **distribution** domain, the number of affected body parts is tallied (potential sum 0–16) and the sum is sorted into five scoring bins: sum of 0–2 = score of 1, sum of 3–5 = score of 2, sum of 6–10 = score of 3, sum of 11–13 = score of 4, and sum of 14–16 = score of 5.

Figure 3: 5-D Itch (Pruritus) Scale



5-D Pruritus Scale

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

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

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

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

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

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

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

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

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

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

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

8.2.19 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'.

A unique health state is defined by combining 1 level from each of the 5 dimensions. A total of 3125 possible health states is defined in this way. Each state is referred to in terms of a 5 digit code. For example, state 11111 indicates no problems on any of the 5 dimensions, while state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression. EQ-5D-5L health states will be converted into a single index value. This index value will be derived using the EQ-5D-5L_Crosswalk_Index_Value_Calculator.v2.xls [van Reenen, 2015].

Index values are defined for several countries. Not all countries participating in this study are available in the Index Value Calculator. For this, the United Kingdom value set is used for all subjects, regardless whether their country is available in the calculator.

If one or more of the 5 dimensions are missing, the index value cannot be derived and is missing as well.

Figure 4: EQ-5D-5L

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

Mobility

I have no problems in walking about	1
I have slight problems in walking about	2
I have moderate problems in walking about	3
I have severe problems in walking about	4
I am unable to walk about	5

Self-Care

I have no problems washing or dressing myself	1
I have slight problems washing or dressing myself	2
I have moderate problems washing or dressing myself	3
I have severe problems washing or dressing myself	4
I am unable to wash or dress myself	5

Usual Activities (*eg, work, study, housework, family or leisure activities*)

I have no problems doing my usual activities	1
I have slight problems doing my usual activities	2
I have moderate problems doing my usual activities	3
I have severe problems doing my usual activities	4
I am unable to do my usual activities	5

Pain/Discomfort

I have no pain or discomfort	1
I have slight pain or discomfort	2
I have moderate pain or discomfort	3
I have severe pain or discomfort	4
I have extreme pain or discomfort	5

Anxiety/Depression

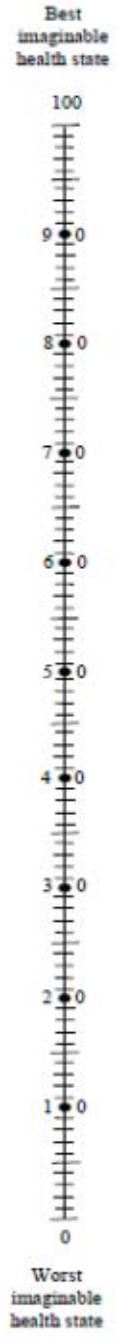
I am not anxious or depressed	1
I am slightly anxious or depressed	2
I am moderately anxious or depressed	3
I am severely anxious or depressed	4
I am extremely anxious or depressed	5

Figure 5: EQ-5D-5L (VAS)

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



8.2.20 WPAI-GH

The subject will answer questions about the effect of his / her health on the ability to work or perform regular activities. General health is defined as any symptoms relating to physical or emotional well-being.

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, ie, worse outcomes, as follows:

Questions:

Q1 = currently employed
Q2 = hours missed due to health problems
Q3 = hours missed other reasons
Q4 = hours actually worked
Q5 = degree health affected productivity while working
Q6 = degree health affected regular activities

Scores:

- Percent **work time missed due to health***: $Q2/(Q2+Q4) \times 100$
- Percent **impairment while working due to health***: $Q5/10 \times 100$
- Percent **overall work impairment due to health***:
  $(Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))\times(Q5/10)]) \times 100$
- Percent **activity impairment due to health**: $Q6/10 \times 100$

If any of the contributing questions for a score is missing, the score cannot be calculated.

* Irrespective of any answers given for Q2 to Q5 these scores will be calculated only if Q1 is answered “YES”.

Figure 6: 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

8.2.21 TSQM-9

The TSQM-9 is a 9-item general instrument that measures the major dimensions of satisfaction with a medication. Scores on the TSQM-9 range from 0 (indicating poor satisfaction) to 100 (indicating perfect satisfaction). Scores on the Effectiveness (3 items), Convenience (3 items), and Global Satisfaction (3 items) scales will be assessed in a cross-sectional manner. If more than one item score is missing, the scale score should not be calculated, and set to missing.

Effectiveness

Effectiveness scale score = [(Item 1 + Item 2 + Item 3 – 3) / 18] × 100
If one item is missing:
Effectiveness scale score = [(Item 1? + Item 2? + Item 3? – 2) / 12] × 100

Convenience

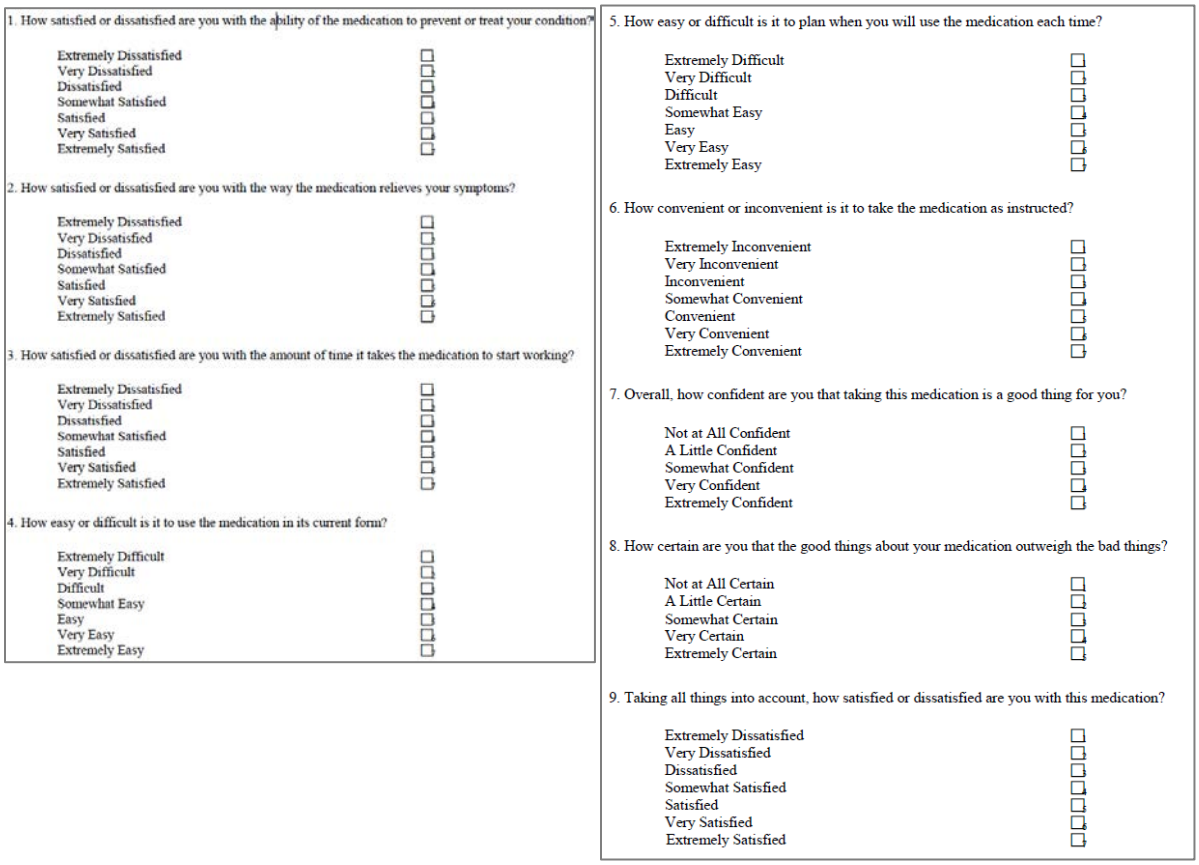
Convenience scale score = [(Item 4 + Item 5 + Item 6 – 3) / 18] × 100
If one item is missing:
Convenience scale score = [(Item 4? + Item 5? + Item 6? – 2) / 12] × 100

Global satisfaction

First recode Item 9: Item 9_R = (Item 9 – 1) × 4/6 + 1

Overall satisfaction scale score = [(Item 7 + Item 8 + Item 9_R – 3) / 12] × 100
If one item is missing:
Overall satisfaction scale score = [(Item 7? + Item 8? + Item 9_R? – 2) / 8] × 100

Figure 7: TSQM-9



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

Extremely Dissatisfied	☐
Very Dissatisfied	☐
Dissatisfied	☐
Somewhat Satisfied	☐
Satisfied	☐
Very Satisfied	☐
Extremely Satisfied	☐

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

Extremely Dissatisfied	☐
Very Dissatisfied	☐
Dissatisfied	☐
Somewhat Satisfied	☐
Satisfied	☐
Very Satisfied	☐
Extremely Satisfied	☐

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

Extremely Dissatisfied	☐
Very Dissatisfied	☐
Dissatisfied	☐
Somewhat Satisfied	☐
Satisfied	☐
Very Satisfied	☐
Extremely Satisfied	☐

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

Extremely Difficult	☐
Very Difficult	☐
Difficult	☐
Somewhat Easy	☐
Easy	☐
Very Easy	☐
Extremely Easy	☐

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

Extremely Difficult	☐
Very Difficult	☐
Difficult	☐
Somewhat Easy	☐
Easy	☐
Very Easy	☐
Extremely Easy	☐

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

Extremely Inconvenient	☐
Very Inconvenient	☐
Inconvenient	☐
Somewhat Convenient	☐
Convenient	☐
Very Convenient	☐
Extremely Convenient	☐

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

Not at All Confident	☐
A Little Confident	☐
Somewhat Confident	☐
Very Confident	☐
Extremely Confident	☐

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

Not at All Certain	☐
A Little Certain	☐
Somewhat Certain	☐
Very Certain	☐
Extremely Certain	☐

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

Extremely Dissatisfied	☐
Very Dissatisfied	☐
Dissatisfied	☐
Somewhat Satisfied	☐
Satisfied	☐
Very Satisfied	☐
Extremely Satisfied	☐

8.2.22 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 (see Figure 8). The total CDASI score is the sum of the total activity score and the total damage score.

Range of total activity score:	0 – 100
Range of total damage score:	0 – 32
Range of total CDASI score:	0 – 132

Figure 8: CDASI

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

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

Extent

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

Gottron's – Hands

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

Periungual

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

Alopecia

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

Total Activity Score
(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)

8.2.23 MDAAT

The MDAAT is a combined tool which will capture the investigator'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.

Extramuscular Global Assessment and Global Disease Activity components are the 2 CSMs used for TIS and DOW calculations.

Figure 9: 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

8.2.24 Study Drug Exposure

There are several levels of aggregation for study drug exposure.

Level 1: Observation in database extract.

Level 2: Infusion. One infusion may consist of more than one eCRF record. If there is more than one eCRF record completed with the same kit number, this is considered an infusion with an interruption. All eCRF records with the same value of Kit Number (as entered in the eCRF) belong to the same infusion.

Level 3: Day with infusions. More than one infusion may be performed on one day. All infusions with the same date of infusion (as entered in the eCRF) belong to the same day of infusion.

Level 4: Week. There can be more than one day with infusions in one week. All infusion days with the same value of Week (as entered in the eCRF) belong to the same week.

Level 5: Period. Weeks 1 to 24 belong to Study Period 1 (Week 1-25), weeks 25 to 52 belong to Study Period 2 (Week 25-53), weeks 53 to End of Study Period 3 belong to Study Period 3 (Week 53-EOP3).

Table 6: Derivation of Exposure Variables

Variable	Observation in database extract	Infusion	Day with Infusion	Week	Period
Planned Total Dose Volume per Week (mL)	n/a	n/a	n/a	entered	n/a
Actual Total Dose (g)	n/a	n/a	n/a	derived	sum
Actual Dose (g/kg bw)	n/a	n/a	n/a	derived	n/a
Duration of infusion	derived	sum	derived	sum	n/a
Duration of treatment	n/a	n/a	n/a	n/a	derived
Administered Volume (mL)	entered	sum	sum	sum	sum

Variable	Observation in database extract	Infusion	Day with Infusion	Week	Period
Total number of infusion sites	entered	max	n/a	n/a	n/a
Volume per Infusion Site (mL)	derived	derived	max	max	max
Infusion Rate per Infusion Site (mL/h)	derived	max	max	max	max
Number of Infusions	n/a	1	sum	sum	sum
Number of Days with Infusions	n/a	n/a	1	sum	sum

derived= see derivation rule below
sum= sum of values of the lower level of the same variable
max= maximum of the values of the lower level of the same variable

Duration

Observation in database extract

$$\text{duration (min)} = \text{end time (min)} - \text{start time (min)}$$

if duration < 0 (ie, end is on the next day) then duration = duration + 24 × 60

Days with infusion

The duration of infusions per day is the sum of the durations of the single infusions. In case of overlapping infusion times the duration of the infusions is the end of the last infusion that contributes to the overlap – the start of the first infusion that contributes to the overlap.

Period

$$\text{duration (days)} =$$

last day of last week with IMP treatment in period – first day of first week in period + 1

Volume per Infusion Site (mL)

Observation in database extract

volume per infusion site (mL) =
administered volume (mL) / total number of infusion sites

Infusion

volume per infusion site (mL) =
administered volume (mL) / total number of infusion sites

Infusion Rate per Infusion Site (mL/h)

Observation in database extract

infusion rate per infusion site (mL/h) =
60 × volume per infusion site (mL) / duration (min)

Actual Total Dose (g)

Week

actual total dose (g) = 200 g/L × administered volume (mL) / 1000

if actual treatment = placebo, then actual total dose (g) = 0

Actual Dose (g/kg body weight)

Week

actual dose (g/kg body weight) = actual total dose (g) / body weight (kg)

body weight = last measurement before first dosing of the week

8.2.25 Prednisolone Equivalent Dose

Before the dose of oral concomitant corticosteroid treatment or oral rescue corticosteroid treatment is used in further derivations, it must be standardized using prednisolone equivalent doses. Each corticosteroid has its own factor ("Equivalent Dose") as shown in Table 7.

dose (mg prednisolone equivalent) = dose (mg) × 20 / Equivalent Dose

Table 7: Corticosteroid Dose Equivalency Table

Corticosteroid (WHO DD Product Name)*	Equivalent Dose	Corticosteroid (WHO DD Product Name)*	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
Meprednisone	16 mg		

* all suffixes like acetate, sodium succinate, sodium phosphate, acetonide can be ignored for programming.

8.2.26 Change of Oral Concomitant Corticosteroid Treatment

The change of oral concomitant corticosteroid treatment compares the average daily doses of the treatment in the reference week and the week of interest. The dose at week 1 (ie, the baseline dose) is the dose administered at the baseline date.

$$\text{average daily dose week X (mg*)} = \text{sum of all daily doses of week X (mg*)} / \text{length week X (days)}$$

If the length of a week is 0 (see Section 8.2.3) the respective average daily dose will be set to the average daily dose of the subsequent week with length > 0.

Change in Week X, for X=2 to 197

$$\text{change (\%)} = 100 \times [(\text{average daily dose week X (mg*)} - \text{baseline dose (mg*)}] / \text{baseline dose (mg*)}$$

* mg prednisolone equivalent

8.2.27 Oral Rescue Corticosteroid Treatment

Oral Rescue Corticosteroid Treatment will be identified via the rescue flag as documented on the 'Oral Corticosteroid Treatment CRF'. Rescue Medication prior to Week 9 is a protocol deviation.

8.2.28 Tapering of Corticosteroid Treatment

The week in which the tapering is initiated will be considered the start of tapering, this will be restricted to Study Period 1.

According to the CSP the taper regimen to be followed depends on the subject's previous stable corticosteroid dose:

CSP Section 5.3.2	Tapering at Week X+1, if
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	$ADD_1 > 10$ and $ADD_X - ADD_{X+2} \geq 2.5$ and $ADD_{X+1} < ADD_X$ and $ADD_X \leq ADD_1$
If stable dose is ≤ 10 mg/day, taper by 1 mg/day every 2 weeks as tolerated	$ADD_1 \leq 10$ and $ADD_X - ADD_{X+2} \geq 1$ and $ADD_{X+1} < ADD_X$ and $ADD_X \leq ADD_1$

ADD_X: average daily corticosteroid dose in mg at Week X

Tapering after rescue corticosteroid treatment is defined as any reduction in the daily concomitant corticosteroid dose compared to the first day of rescue corticosteroid treatment.

8.2.29 Timed up and go

In case of multiple measurements per subject per visit the minimum result will be used. Analysis will be based on the following categories for timed up and go [Podsiadlo et al, 1991]:

- <10 seconds: completely independent
- ≥10-<20 seconds: independent for main transfers
- ≥20 seconds: requires assistance

8.3 Study Periods Relative to Treatment

Definitions of the start and end of periods and reference visits are presented in Table 8 and Table 9.

Note: If some of the core set measures assessed at the Baseline/Week 1 or the Week 25 visit were assessed after start of IMP at the respective visit but within 5 days after start, the core set measures will be considered baseline assessments or included in the TIS calculation for Week 25 or Week 53, respectively. All these cases will be presented during the BDRM. The same approach will be applied for all other data collected in eCOA data.

Table 8: Periods and Reference Visits for Study Periods 1 and 2

Period	Start of period	Reference visit of period	End of period[a]
For efficacy analysis (TIS):			
Week 1 – Week 25 (Week 1 - EOP1)	Start date and time of the first IMP infusion	Baseline (before infusion of IMP)	Week 25 (before infusion of IMP)
Week 25 – 53/Week 56[b] (Week 25 - EOP2)	Start date and time of the first IMP infusion at Week 25	Baseline (before infusion of IMP)	Week 53 (before infusion of IMP)/Week 56
For efficacy analysis (all other endpoints):			
Week 1 – Week 25 (Week 1- EOP1)	Start date and time of the first IMP infusion	Baseline (before infusion of IMP)	Week 25 (before infusion of IMP)
Week 25 – Week 53/Week 56[b] (Week 25 - EOP2)	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 safety analysis:			
Week 1 – Week 25	Start date and time of the first IMP infusion	Baseline (before infusion of IMP)	Week 25 (before infusion of IMP)

Period	Start of period	Reference visit of period	End of period[a]
(Week 1 - EOP1)			
Week 25 – Week 53/Week 56[b] (Week 25 - EOP2)	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
Week 1 – Week 53/Week 56[b] (Week 1 - EOP2)	Start date and time of the first IMP infusion	Baseline (before infusion of IMP)	Week 53 (before infusion of IMP)/Week 56

[a] The end of the period is the listed visit or the last visit before / at withdrawal. For efficacy, the assessments within 7 days following the IMP discontinuation will be included in the analysis if no rescue medication was administered before the respective assessment (see Section 8.2.3). Efficacy assessments for subjects who withdraw from IMP for reasons related to the Ukraine war that are assessed more than 6 weeks after the last IMP administration will be set to missing (see Section 10.2).

[b] 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). No efficacy measures will be collected at Week 56.

Table 9: Periods and Reference Visits for Study Period 3

Period	Start of period	Reference visit of period	End of period[a]
Week 53 – EOP3	Start date and time of the first IMP infusion at Week 53	Week 53 (before infusion of IMP)	EOP3

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

8.3.1 Study Time Periods for Adverse Events

Adverse events (AEs) with onset date/ time after start of first infusion of IMP are TEAEs. Assessment whether an AE is considered treatment-emergent, will take place after imputation of partially missing dates (see Section 8.1.2).

The TEAE analysis will be done for the periods and groups shown in Section 11. An AE will be counted for the analysis of a period if the onset of the event falls within the period. For the definition of start and end of the periods see Table 8 and Table 9.

8.3.2 Study Time Periods for Concomitant Medications

The following classification of concomitant medication related to start date and the end date of IMP will be applied. Each medication belongs to one of the following categories:

- Assign to 'Prior' if the medication end date is before the date of the first IMP infusion.
- Assign to 'Concomitant in Period 1' if the medication start date is at or before start of first IMP infusion at Week 25 or the medication start date is at or before the end of the last IMP infusion in Period 1 AND the medication end date is at or after start of first IMP infusion at Week 1.
- Assign to 'Concomitant in Period 2' if the medication start date is at or before start of first IMP infusion at Week 53 or the medication start date is at or before the end of the last IMP infusion in Period 2 AND the medication end date is at or after start of first IMP infusion at Week 25.
- Assign to 'Concomitant in Period 3' if the medication start date is at or before the end of last IMP infusion in Period 3 AND the medication end date is at or after start of first IMP infusion at Week 53.
- Assign to 'Post' if the medication start date is after the date of the last IMP infusion

If a start or stop date is partially missing, the imputation takes place before the classification of the medication in the categories above.

8.3.3 Study Time Periods for Medical History

Prior medical conditions are those which end before the start of first infusion of IMP. All other Medical History entries are Concomitant medical conditions, including those with missing end date.

8.4 Values of Potential Clinical Importance

Not applicable.

9 Study Population

Unless otherwise stated, all tables and listings in this section will be based on the mITT analysis set, and all summaries and data listings will use treatment labels as specified in Section 7.2.

9.1 Disposition of Subjects

The following summaries will be provided by treatment sequence, period and overall (if applicable). Summaries for subject and IMP status will also be provided for the subgroup of Japanese subjects:

- Subjects in each of the analysis sets described in Section 6.
- Subject status, including
    - subjects screened,
    - screen failures (including the reason),
    - subjects randomized,
    - completed IMP,
    - discontinued IMP (including the primary reason)
    - completed the study, and
    - withdrawals from the study (including the primary reason).
- IMP status, including
    - completed subjects,
    - prematurely discontinued subjects (including the primary reason).

Reasons for study withdrawal and IMP discontinuation will be presented in the order they are displayed in the electronic Case Report Form (eCRF).

The following listings will be provided:

- Subjects excluded from analysis sets by analysis set
- Reasons for study withdrawal including the date of withdrawal

Precise selection of protocol deviations to identify subjects to exclude from the PP analysis set and the PK analysis set will be defined and documented in the minutes of the BDRM before unblinding the study for the primary data analysis (ICH E9) (see Section 2).

9.2 Protocol Deviations

The following summaries will be provided by treatment group:

- Inclusion and exclusion protocol deviations.
- All major protocol deviations including inclusion and exclusion, with each protocol deviation classified as 'Deviation that requires exclusion from per-protocol analysis set' and as 'Deviation that requires exclusion from PK analysis set'.

The following listings will be provided:

- All inclusion and exclusion protocol deviations.
- All other protocol deviations

9.3 Demographic and Baseline Characteristics

All demographic and Baseline characteristics summaries will be based on the mITT, PP, mITT-Ex, and PK analysis sets and the SAF-P3 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.

The following summaries will be provided by treatment sequence and overall. These summaries will also be provided for the subgroup of Japanese subjects in the mITT analysis set:

- Demographic characteristics
    - Age (years)
    - Age group (18-64, ≥ 65 years)
    - Sex
    - Ethnicity
    - Race and racial combinations
    - Body weight, baseline assessment (kg)

  - Height (cm)
  - BMI, baseline assessment (kg/m²)
  - Prior IgG treatment (identified by ATC 3 =“IMMUNOGLOBULINS")
- Disease characteristics at Screening
- Prior medical conditions
- Concomitant medical conditions

The following summaries of the number and percentage of subjects in each stratum will be provided:

- Region (Japan vs. non-Japan)
- Baseline MMT-8 (≤ 142 points vs. > 142 points)

The following listings will be provided:

- Demographic characteristics
- Race and racial characteristics
- Disease characteristics at Screening
- Prior and concomitant medical conditions

9.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded using WHO Drug Dictionary Enhanced (WHO-DDE) 2018 Mar B3 or more recent version, summarized, and listed. The summary of concomitant medications will show the number and percentage of subjects taking prior and concomitant medications. Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information will be included in the data set created but will not appear on the listing or summary.

In the summary of concomitant medications, each subject is counted once within each unique term. For example, if a subject takes Amoxicillin on two separate occasions, the subject is counted only once under the ingredient “Amoxycillin”.

Summaries for the following categories will be provided:

- Prior Medication (including corticosteroids) for mITT
- Concomitant Medication (including corticosteroids) for mITT, mITT-EX and for SAF-P3
- Prior Medication (including corticosteroids) to Treat Dermatomyositis for mITT
- Concomitant Medication to Treat Dermatomyositis, excluding Oral Corticosteroids for mITT and mITT-EX
- Oral Rescue Corticosteroid Treatment for mITT
- Oral Concomitant Corticosteroid Treatment, Excluding Oral Rescue Treatment for mITT

9.5 Non-Pharmacological Interventions and Physiotherapy

A listing for non-pharmacological interventions, physiotherapy, and change of physiotherapy will be provided.

10 Efficacy

This section describes the planned analyses of efficacy endpoints. mITT will be the primary analysis set for the analysis of all efficacy endpoints. PP will be the supportive analysis set for the primary and key secondary efficacy endpoint.

10.1 Primary Estimand

The primary interest is to quantify the treatment effect of IgPro20

- where the potential confounding effect of oral rescue corticosteroid treatment is excluded
- where the potential confounding of subjects who withdraw from treatment or 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,; ICH E9 (R1), 2020].

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 and have post baseline efficacy results in Study Period 1 (mITT). See Section 6 for details.
- Variable: responder status based on TIS assessments at Weeks 17, 21, and 25
- Intercurrent events:
    - withdrawal from randomized IMP or the study, which is not related to the Ukraine war, or receiving oral rescue corticosteroid treatment before Week 25 is considered treatment failure
    - withdrawal from randomized IMP or the study which 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

10.2 Analysis of Primary 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 10.1, a responder is defined as a subject with a TIS ≥ 20 points at Week 25 and at least at 1 of the previous scheduled visits (Week 17 or Week 21) who completes 24 weeks of randomized IMP treatment without the use of oral rescue corticosteroid treatment.

Therefore, for subjects who do not withdraw from IMP or the study for reasons which 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 oral rescue corticosteroid treatment before Week 25 (Note: for subjects with corticosteroid taper starting at Week 17, 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)

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 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 (MAR) 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. 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 6).

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

(1) Imputation step

- 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 a Markov Chain Monte Carlo (MCMC) method 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 post-dropout missing values 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. If

including country in the imputation model is not possible due to the sparseness of the data the variables Region (1): Japan, non-Japan and Region (2): USA, non-USA will be included.

- In each of the data sets subjects' responses will be derived according to the definition provided above.
- The same multiple imputation process will be done for subjects who completed Study Period 1 without the use of oral rescue corticosteroid treatment but have missing TIS values.
- 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.

(2) Analysis step for completed datasets

- For each of the 50 datasets 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 (≤ 142 points vs. >142 points).

(3) Pooling /combining step dataset

- 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% confidence interval (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 also be provided for the subgroup of Japanese subjects.

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 MMT-8 > 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.

10.2.1 Sensitivity and Supplementary Analyses of Primary 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. All sensitivity analyses will be done based on the imputed TIS data used for the primary efficacy analysis and combined using Rubin's rule. Consistency of findings from the primary and sensitivity or supplementary analyses will be investigated and clinical plausibility of findings will be examined. Sensitivity analyses will address the following aspects:

- *(1) Standard Logistic Regression*
  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.
- (*2) Responder status of withdrawals not due to lack of efficacy or IMP related AEs based on last TIS values*
  Sensitivity to the assumption that all early dropouts for reasons which are not related to the Ukraine war before Week 25 are non-responders will be assessed in this analysis. The responder status of subjects withdrawn from the study for reasons which are not related to the Ukraine war 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
- (*3) Responder status of withdrawals not due to lack of efficacy or death based on MI*
  Sensitivity to the assumption that all early dropouts for reasons which are not related to the Ukraine war before Week 25 are non-responders will be assessed in this analysis.
  - The responder status of subjects withdrawn from the study due to lack of efficacy or for subjects who die during study period 1 will be set to "non- responder"
  - Data of all other subjects who are withdrawn from the study will be handled with the multiple imputation approach as described in Section 10.2.

- *(4) Exclusion of subjects dropping out due to the Ukraine war:*
  An additional sensitivity analysis will be done excluding subjects who drop out for reasons related to the Ukraine war using the same method as in Section 10.2.
- *(5) Responder status in subjects who have received increased oral corticosteroids without meeting DOW based on TIS results*

A supplementary analysis will address the following:

- *(1) Worsening of specific CSMs considered non-response – exclusion of subjects with dropping out due to the Ukraine war or subjects with missing TIS at Weeks 17 to 25*
  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). Subjects who completed Study Period 1 without the use of oral rescue corticosteroid treatment but have missing TIS values at Week 17, Week 21 or Week 25 will also be excluded from this analysis, except if response can be unambiguously determined by available data (eg, if TIS at Week 17 or Week 21 is missing but TIS at Week 25 is less than 20 points).

  Note for clarification: a responder is defined as a subject with a response according to the above mentioned criteria at Week 25 and at least at 1 of the previous scheduled visits (Week 17 or Week 21) who completes 24 weeks of randomized IMP treatment without the use of oral rescue corticosteroid treatment.
- *(2) Threshold for TIS response in primary endpoint increased to 40*

The analytical approach in the sensitivity and supplementary analyses will be the same as in the primary endpoint analysis. These analyses will be based on the mITT and PP.

10.2.2 Subgroup Analyses of Primary Endpoint

Internal consistency of observed treatment effect across major subgroups on the primary endpoint will be investigated as part of exploratory analyses. Subgroup factors are shown in the list below:

- Age: < 65 years, ≥ 65 years
- Age at initial diagnosis of DM: < 18 years, ≥ 18 to < 40 years, ≥ 40 years
- Gender: Female, Male
- Baseline MMT-8: MMT-8 ≤ 142 points, MMT-8 >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.
- Region (1): Japan, non-Japan
- Region (2): USA, non-USA
- Disease severity:
  - Mild (Physician Global Disease Activity VAS ≥ 2 cm and < 4.5 cm)
  - Moderate (Physician Global Disease Activity VAS ≥ 4.5 cm and < 7.5 cm)
  - Severe (Physician Global Disease Activity VAS ≥ 7.5 cm)

Subgroup analysis will use the same analytical approach as in the primary endpoint analysis. For each of the imputed data sets the 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 (≤ 142 points vs. >142 points) and the corresponding results across the imputed data sets are combined for overall inference using Rubin's rule. The test results will be summarized for each level of subgroup, including at least the following: the number of subjects by treatment, the number (%) of responders by treatment, 95% CI for % of responders by treatment; odds ratio with 95% exact CI and one-sided p-value. A forest plot of subgroups with odds ratio and 95% CI displayed for each level of subgroup will be provided.

10.3 Key Secondary Estimand

The key secondary interest is to quantify the treatment effect of IgPro20 under the hypothetical situation where no subjects receive oral 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). For details see Section 6.
- 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 oral rescue corticosteroid treatment before Week 25, data after withdrawal or oral 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 6.
- Variables: reduction of oral concomitant corticosteroid dose at Week 25
- Intercurrent events:
    - withdrawal from randomized IMP or the study, which is not related to the Ukraine war, or receiving 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 randomized IMP or the study which is 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 Analysis of Key Secondary Endpoints

The following key secondary efficacy endpoints are defined:

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

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

- TIS at Week 25: treatment, visit, the interaction between treatment and visit, region, and Baseline MMT-8 stratification variable (≤142 points vs. >142 points) as fixed effects, subjects as a random effect;
- Changes from Baseline MMT-8 at Week 25: treatment, visit, the interaction between treatment and 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, visit, the interaction between treatment and visit, region, and Baseline MMT-8 stratification variable (≤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 group will also be presented along with their standard errors.

Only data collected up to the end of Period 1 will be included in the MMRM analysis. For subjects who receive oral rescue corticosteroid treatment or who withdraw from treatment or the study, data after the first administration of oral rescue corticosteroid treatment or withdrawal from randomized IMP treatment will be considered missing and thus not included in 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 10.2. The oral concomitant corticosteroid dose at Week 25 will be considered to be reduced by at least 25% when the

average daily dose of Week 24 is reduced by at least 25%, as treatment with IgPro20 starts in both treatment sequences on the first day of Week 25.

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 (MAR) 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 weeks 17 to Week 24 (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 10.2. 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 24, 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 (≤ 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. The key secondary analyses will be performed based on the mITT and repeated for the PP.

Table 10: Key Secondary Analysis – Summary Measures

Endpoint	Summary Measures
TIS at Week 25	• Mean TIS values at Week 25 by treatment sequence • Point estimates and 95% CI from MMRM for mean difference (IgPro20 – Placebo) at Week 25
Change from Baseline in MMT-8 at Week 25	• Mean changes from baseline in MMT-8 at Week 25 by treatment sequence • Point estimates and 95% CI from MMRM for mean changes difference (IgPro20 – Placebo) at Week 25
Change from Baseline in 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 from MMRM for mean changes difference (IgPro20 – Placebo) at Week 25
Reduction of oral concomitant corticosteroid dose at Week 25	• Point estimate and 95% CI of percentage of subjects who are able to reduce the oral concomitant corticosteroid dose by ≥ 25% at Week 25 by treatment sequence • Point estimates and 95% CI for the odds ratio (IgPro20 : placebo) at Week 25

10.4.1 Sensitivity Analyses of Key Secondary Endpoints

A tipping point analysis as described in Ouyang, 2017 will be performed as a sensitivity analysis for the continuous key secondary endpoints.

- Tipping point analysis using all available data up to Week 25
  The base case for the tipping point analysis is to include all available data as collected in the MMRM analysis.

  - Replace missing values of scheduled visits which are between two visits with non-missing values ("intermittent missing values") using the MCMC option in SAS PROC MI by treatment group 50 times to create 50 data sets with only monotone missings.

  - Replace missing values arising after the last scheduled visit ("trailing missing values") with non-missing values using PROC MI statement using covariates and values from previous visits (1 imputation) regardless of the reason for discontinuation. The result of this imputation will be stored in a separate analysis data set.

- Obtain delta as treatment difference (IgPro20 – placebo) for each post-baseline visit from original MMRM. There will be a separate delta for each visit.
- Repeat for k = 0%, 100%, 120%, 140%, …
  - Subtract k × delta from the imputed trailing values of the IgPro20 arm. Subtraction should stop for an individual value at the worse bound of the variable, ie, at
    - TIS = 0 (lower is worse, values below 0 are not possible),
    - Change from Baseline MMT-8 = – baseline value (lower is worse, changing to below 0 is not possible),
    - Change from Baseline CDASI total activity score = 100 – baseline value (higher is worse, changing to above 100 is not possible)
  - Calculate the MMRM for the 50 imputed data sets and combine the 50 results using PROC MIANALYZE.
  - Stop if one-sided p-value exceeds the significance level according to the Hommel procedure for the respective key secondary endpoint (see Section 4.2.2) or if the worst case imputation for all missing values is reached. The tipping point analysis will only be performed for a variable if the main analysis shows a significant p-value (see Section 4.2.2).
- Obtain k at a precision of 1% by iteration.

- Tipping point analysis excluding data after rescue treatment or withdrawal from IMP
  The tipping point analysis will be repeated under the above-mentioned hypothetical estimand, ie, where data obtained after oral rescue corticosteroid treatment or withdrawal from IMP are excluded from the MMRM analysis.
  - Set all data obtained after oral rescue corticosteroid treatment or withdrawal from IMP for any reason to missing
  - Perform all steps described for the first tipping point analysis above.

10.4.2 Subgroup Analyses of Key Secondary Endpoints

For the key secondary endpoints subgroup analysis will be done for region (see Section 10.2.2) and for Baseline MMT-8 (≤ 142, >142).

Subgroup analysis will use the same analytical approach as in the key secondary analysis. For the continuous key secondary endpoints, one MMRM will be performed for each level of subgroup. The test results will be summarized for each level of subgroup, including at least the following: the number of subjects by treatment, the Least Square mean (LS-mean) by treatment, 95% CI for LS-mean by treatment; difference of LS-means with 95% CI and p-value.

10.5 Analysis of Secondary Efficacy Endpoint

All secondary efficacy analyses will be performed for the following periods and analysis sets:

- Week 1-25 by treatment sequence (mITT)
- Week 25-53 by treatment sequence (mITT-Ex)

Raw data and changes from the reference visit will be summarized at all visits as appropriate (Table 11). 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 descriptive.

Continuous variables

- Absolute values and changes from reference visit will be summarized in terms of the number of observations, mean, standard deviation, median, Q1, Q3, minimum, and maximum. A virtual timepoint will be added that describes the last individual visit for each subject per period.

- A MMRM model similar as described in Section 10.4 will be applied. This will be done for each period separately, taking only the visits of the respective period into account. An additional covariate will be the value of the variable at the reference visit of the respective period. The MMRM will analyze the changes from the reference visit.

TIS

- Absolute values will be summarized in terms of the number of observations, mean, standard deviation, median, Q1, Q3, minimum, and maximum.
- A MMRM model similar as described in Section 10.4 will be applied. This will be done for each period separately, taking only the visits of the respective period into account. An additional covariate will be the value of TIS at Week 25 for the analysis of period Week 25-53. The MMRM will analyze the absolute values.

Time to event variables

- The time to event is calculated by period between the date of event minus the date of the respective reference visit. If the event did not occur in the respective period, the subject is considered censored for the period. The time of censoring for the different endpoints is defined in the table below:

Endpoints	• Time to first achieving TIS ≥ 20/40/60 points • Time to meeting DOW for the first time the time	• Time to first intake of oral rescue corticosteroid treatment
Time of censoring	• For subjects receiving rescue medication in the period: Date of last assessment of the CSMs (in eCOA) in the respective period before or at the date of starting rescue medication • For subjects not receiving rescue medication in the period: Date of last assessment of the CSMs (in eCOA) in the respective period	• End date of the respective period or • Last day of last week with IMP intake in case of IMP discontinuation in the period

	Note: the assessment following IMP discontinuation may be included, the acceptable time window will be defined in the BDRM (see Section 8.2.3).	

In addition to the analyses for Study Period 1, an overall analysis for the combined Study Period 1 and 2 will be performed.

- The time to event will be summarized in terms of the number of observations, number of censored observations, median, Q1, Q3, and the life table output showing the Kaplan-Meier estimates.

- A Cox regression model will be applied for Study Period 1. The model includes effects for treatment, region (Japan vs. non-Japan), and Baseline MMT-8 (≤ 142 points vs. >142 points). The Cox regression will not be done for the whole study duration, as no proportional hazard can be expected.

- An additional exploratory analysis will be added for time to first sustained improvement for each of the categories minimal improvement (TIS ≥ 20), moderate improvement (TIS ≥ 40), major improvement (TIS ≥ 60). Sustained improvement is defined as follows:

    - Improvement met and no oral rescue medication during study period 1 and improvement at Week 25.
      For the calculation of "Time to first sustained improvement" the date of the first time the respective improvement category is met will be used.

    - Subject receiving oral rescue medication or subjects not showing improvement at Week 25 will be considered as not improved and will be censored at the date of last assessment of the CSMs (in eCOA) in study period 1.

    - Subjects discontinued early (without receiving oral rescue medication) will be considered as not improved and will be censored at the date of last assessment of the CSMs (in eCOA) in study period 1.

Response variables

- Response variables will be summarized using frequency counts and percentages per visit or period as indicated in Table 11.
- An exact logistic regression model similar to the model described in Section 10.2 will be applied. No odds ratios will be calculated for the variables "Subjects meeting DOW at least twice per period" and "Subjects meeting DOW more than twice per period".

Cumulative distribution function

- Change from reference visit will be summarized using frequency counts of levels of improvements/worsening,
- The Kolmogorov-Smirnov test will be used to test the equality of the two distribution functions.

Table 11: Secondary Efficacy Endpoints - Variables

Endpoint	Variable	Type of summary measure
TIS from Week 5 to Week 53	• TIS values	• continuous
	• Subjects achieving TIS $\geq$ 20 points per visit • Subjects achieving TIS $\geq$ 40 points per visit • Subjects achieving TIS $\geq$ 60 points per visit • Subjects achieving TIS $\geq$ 20 points at the end of Study Period 2	• response
	• Time to first achieving TIS $\geq$ 20 points • Time to first achieving TIS $\geq$ 40 points • Time to first achieving TIS $\geq$ 60 points	• time to event
CDASI from Baseline to Week 53	• CDASI total activity score Note: For Study Period 2 changes from baseline will also be calculated	• continuous
CSMs (except muscle enzymes) from Baseline to Week 53	• Physician Global Disease Activity • Patient Global Activity • MMT-8 • HAQ-DI • Extramuscular global activity	• continuous

Endpoint	Variable	Type of summary measure
	Note: For Study Period 2 changes from baseline will also be calculated	
DOW from Baseline to Week 53	• Subjects meeting DOW at least once per period • Subjects meeting DOW at least twice per period • Subjects meeting DOW more than twice per period	• response
	• Time to meet DOW for the first time	• time to event
	• Subjects meeting DOW followed by oral rescue corticosteroid treatment per period	• response
Oral rescue corticosteroid treatment (from Baseline to Week 25)	• Subjects receiving oral rescue corticosteroid treatment • Subjects whose oral rescue corticosteroid treatment is tapered	• response
	• Time to first intake of oral rescue corticosteroid treatment	• time to event
EQ-5D-5L from Baseline to Week 53	• Mobility • Self-care • Usual Activities	• cumulative distribution function
Reduction of oral concomitant corticosteroid treatment from Baseline to Week 53	• Subjects who start oral concomitant corticosteroid dose taper before Week 25, ie, there is a reduction in week 24 • Subjects who are able to reduce the oral concomitant corticosteroid treatment at the end of each period by o ≥ 25% o ≥ 50% o ≥ 75%	• response

The following additional analyses will be provided:

- For the most abnormal muscle enzyme (CSM 5) summarizing analysis will be provided for the absolute percent change from baseline to Week 53 in analogy to the analyses for the other CSMs.

- For subjects with available TIS at Week 25 it will be investigated in how many CSMs improvement was achieved. This analysis will be done by TIS improvement category at Week 25 (TIS ≥ 20, TIS ≥ 40, TIS ≥ 60).

- For subjects with a baseline CDASI Total Activity Score > 0, the proportion of subjects showing an improvement of more than 35% from baseline will be provided per visit. The corresponding analysis will also be done for the subgroup of patients with

    - baseline CDASI Total Activity Score ≤ 14 and > 0

    - baseline CDASI Total Activity Score > 14

10.6 Analysis of Exploratory Endpoints

The exploratory endpoints for Study Period 1 and Study Period 2 listed in Table 12 will be summarized descriptively similarly to secondary efficacy endpoints as described in Section 10.5. No comparison between treatment sequences will be done.

Table 12: Exploratory Endpoints – Variables (Study Period 1 and Study Period 2)

Endpoint	Variable	Type of summary measure
EQ-5D-5L	• Pain/ discomfort • Anxiety/ depression	• cumulative distribution function
	• Utility index • Health VAS	• continuous
WPAI-GH	• Percent work time missed due to health • Percent impairment while working due to health • Percent overall work impairment due to health • Percent activity impairment due to health	• continuous
TSQM-9	• Effectiveness • Convenience • Global Satisfaction • Item 1 to Item 9 Change from Baseline will not be summarized as there is no Baseline assessment for TSQM-9.	• continuous

Endpoint	Variable	Type of summary measure
Timed Up and Go	• Timed Up and Go	• categorical (see Section 8.2.29)
5-D Itch score	• Total score	• continuous
Muscle enzymes	Serum levels of • CK (IU/L) • LDH (IU/L) • AST (IU/L) • ALT (IU/L) • aldolase (IU/L)	• continuous
Serum IgG	• IgG serum concentrations	• continuous
	• IgG PK parameters C_{max}, C_{trough}, and AUC	• see Section 12
IIM autoimmune antibody panel	• MSA • MAA • ANA	• Response, categorical, continuous
HAQ	• Pain VAS	• continuous
MDAAT	• VAS Constitutional Disease Activity • VAS Cutaneous Disease Activity • VAS Skeletal Disease Activity • VAS Gastrointestinal Disease Activity • VAS Pulmonary Disease Activity • VAS Cardiovascular Disease Activity • VAS Other Disease Activity	• continuous
CDASI	• Total score • Total damage score	• continuous
Reduction of oral concomitant corticosteroid treatment	• Percent reduction of average daily dose	• continuous

The exploratory endpoints listed in Table 13 for Study Period 3 will be summarized descriptively only as described in Section 10.5. The data will be presented by sequence and overall including

visits from all 3 study periods based on the SAF-P3. Reference visits are described in Section 8.2.1.

Table 13: Exploratory Endpoints – Variables (Study Period 3)

Endpoint	Variable	Type of summary measure
CSMs	• Physician Global Disease Activity • Patient Global Activity • MMT-8 • HAQ-DI	• continuous
HAQ	• Pain VAS	• continuous
CDASI	• Total activity score • Total score • Total damage score	• continuous
EQ-5D-5L	• Mobility • Self-care • Usual Activities • Pain/ discomfort • Anxiety/ depression	• cumulative distribution function
	• Utility index • Health VAS	• continuous
Corticosteroid treatment	• Percent reduction of average daily dose	• continuous

10.7 Treatment Compliance

Treatment compliance will be summarized for each period, by treatment sequence using descriptive statistics. The number and percentage of subjects who are compliant or non-compliant will be presented for each period.

Weekly treatment compliance with assigned IMP is determined using the algorithm:

$$\text{compliance (\%)} = (\text{actual volume infused/planned volume}) \times 100.$$

A subject will be considered to be compliant with the assigned IMP for the week if the weekly compliance is between 80% and 120%. If a subject's weekly compliance is less than 80% or greater than 120%, he/she will be considered to be non-compliant with the assigned IMP for that week.

For the duration of each period of a subject overall, the subject will be considered to be compliant with the assigned IMP if he/she is compliant for at least 80% of his/her duration of that period. If the subject is non-compliant at more than 20% of his/her duration, then he/she will be considered to be non-compliant with the assigned IMP for that period.

11 Safety Analyses

All Safety analyses will be performed for the following periods and analysis sets:

- Week 1-EOP1 by treatment sequence (SAF)
- Week 25-EOP2 by treatment sequence (SAF-Ex)
- Week 53-EOP3 by treatment sequence (SAF-P3)

Additionally, adverse events will be presented using the following periods and analysis sets:

- IgPro20 Periods (SAF-IgPro20)
  Note: This is restricted to IgPro20 treatment

11.1 Extent of Exposure

Exposure to the investigational product will be descriptively summarized by period and treatment sequence:

- Duration of exposure (days) per subject*
- Number of infusions (partial or complete) administered per subject*
- Number of days with infusions per subject*
- Total dose received (g) per subject*
- Total volume received (mL) per subject*
- Maximum volume per infusion site (mL) (categorized) per days with infusions*
- Maximum volume per infusion site (mL) (continuous) per weeks with infusions, per days with infusions, and per infusion
- Maximum infusion rate per infusion site (mL/h) (categorized) per days with infusions*
- Maximum infusion rate per infusion site (mL/h) (continuous) per weeks with infusions, per days with infusions, and per infusion
- Actual total volume (mL) per weeks with infusions, per days with infusions, and per infusion

- Actual total dose (g/kg body weight) per weeks with infusions
- Duration of infusion (minutes) per weeks with infusions, per days with infusions, and per infusion
- Number of infusion sites per infusion
- Overall compliance per subject*
- Percentage of subjects requiring additional infusion training in Week 3 or Week 4

Analyses marked with * will also be provided for the subgroup of Japanese subjects.

Following data will be summarized for each week by treatment sequence:

- Actual total volume (mL) per subject
- Actual total dose (g/kg body weight) per subject
- Maximum volume per infusion site (mL) per subject
- Maximum infusion rate per infusion site (mL/h) per subject
- Duration of infusion (minutes) per subject

The listing of individual subject data will include all variables presented in the summary tables.

11.2 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher. TEAEs are defined as AEs started after the start of the first infusion of IMP. All AEs regardless of when they were reported will be listed.

In addition to an overall TEAE analysis, the analysis will be repeated for each period. An AE will be counted in the respective analysis, if the onset of the event falls within the period. For the definition of start and end of the periods see Table 8 and Table 9.

- An overview summary of TEAEs, including number of subjects, percentages of subjects, the number of events, and TEAE rate per time at risk, including the following. This summary will also be provided for the subgroup of Japanese subjects and by age group (<65 year, ≥65 years):
  - 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 IMP
- Temporally associated AESIs (defined as an 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
- Fatal serious TEAEs

- The following descriptive tables will be generated for TEAEs, including number of subjects, percentages of subjects, the number of events, and TEAE rate per time at risk. Analyses marked with * will also be provided for the subgroup of Japanese subjects:
  - TEAEs by System Organ Class (SOC) and Preferred Term (PT)
    Note: This table will also be provided by age group (<65 year, ≥65 years)
  - 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

- All AE summaries presented by SOC and preferred term will include a virtual SOC comprising of local reactions, ie, all AEs reported within the MedDRA High level terms “Administration site reactions NEC” or “Infusion site reactions” or “Injection site reactions”. Local reactions will be analyzed by using a virtual SOC called “local adverse events”.

- All AE summaries presented by SOC and preferred term will include a virtual SOC "Thromboembolic Events" comprising all AEs reported within the MedDRA SMQs in Section 11.3.

All tables will be displayed in descending order of total incidence by preferred term and by SOC and PT, respectively.

TEAE rates per time at risk will be calculated as annualized TEAE rates using:

$$Annualized\ TEAE\ rate = \frac{number\ of\ events}{(Total\ observational\ time\ in\ this\ period\ (days)\ /\ 365.25)}$$

Number of events and total observational time are counted within the respective period and treatment group. Start dates and end dates to derive the observational time for the respective periods are defined in Table 8 and Table 9.

Temporally associated TEAEs are defined as AEs with an onset between the start of the infusion and up to 72 h after the end of IMP infusion. In case time of onset of AE is missing, the AE is considered temporally related, if the onset of the AE is between the day of the start of infusion and the day of the end of infusion + 3 days (inclusive).

The following listings will be provided:

- All Adverse Events
- All serious TEAEs

11.3 Adverse Events of Special Interest (AESI)

In this study, TEEs will be treated as AESIs. The following 3 narrow standardized 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

In addition to the comprehensive search by MedDRA SMQs, the site enters their assessment in the eCRF on whether the AE is of special interest. These entries are listed but not summarized.

The potentially elevated risk of IgPro20 TEEs over placebo will be evaluated by the IDMC. The IDMC will assess whether a TEE counts towards the stopping rule. Only the TEEs counting towards the stopping rule will be included in this analysis.

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 and the possibility of no TEEs in either treatment group. The analysis will include data from Study Period 1 and Study Period 2.

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

Point estimates for the relative risk and the upper and lower limit of the corresponding (1-α) credibility interval will be calculated as follows:

$$RR = \left(\frac{TEE_{IgPro20} + 1}{TEE_{Pbo} + 1} \times \frac{T_{Pbo}}{T_{IgPro20}}\right) \times F(2TEE_{IgPro20} + 2, 2TEE_{Pbo} + 2, 0.5)$$

$$RR_{LL\ CI} = \left(\frac{TEE_{IgPro20} + 1}{TEE_{Pbo} + 1} \times \frac{T_{Pbo}}{T_{IgPro20}}\right) \times F\left(2TEE_{IgPro20} + 2, 2TEE_{Pbo} + 2, \frac{\alpha}{2}\right)$$

$$RR_{UL\ CI} = \left(\frac{TEE_{IgPro20} + 1}{TEE_{Pbo} + 1} \times \frac{T_{Pbo}}{T_{IgPro20}}\right) \times F\left(2TEE_{IgPro20} + 2, 2TEE_{Pbo} + 2, 1 - \frac{\alpha}{2}\right)$$

With

RR:	Point estimate for the relative risk of experiencing a TEE under IgPro20 compared with placebo
$RR_{LL\ CI}$:	Lower limit of the (1-α) credibility interval for RR
$RR_{UL\ CI}$:	Upper limit of the (1-α) credibility interval for RR
$TEE_{IgPro20}$:	Total number of TEEs that count towards the stopping rule under IgPro20
TEE_{Pbo}:	Total number of TEEs that count towards the stopping rule under placebo
$T_{IgPro20}$:	Total observational time (days) over all subjects treated with IgPro20

T_{Pbo}: Total observational time (days) over all subjects treated with placebo

F(d1, d2, alpha): alpha-quantile of the F distribution with parameters d_1 and d_2

As the data can neither be completely cleaned nor complete at the time of IDMC analyses following the occurrence of a TEE, assumptions and derivation of total observational time are described in detail in the IDMC analysis plan.

11.4 Pregnancies

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If any subject becomes pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

11.5 Clinical Laboratory Evaluations

The following laboratory tests will be summarized as described in this section:

Hematology: hemoglobin, hematocrit, platelets, erythrocytes, leukocytes with differential counts (neutrophils, basophils, eosinophils, lymphocytes, monocytes), reticulocytes, hemoglobin A1c

Biochemistry: sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), glucose, gamma-glutamyl transferase (GGT), alkaline phosphatase, creatinine, CK, LDH, AST, ALT, aldolase

Coagulation: D-dimer

Virology: Human immunodeficiency virus (HIV-1, HIV-2), Hepatitis B virus (HBV), and Hepatitis C virus (HCV)

Additional lab tests for hemolysis criteria: AB0 blood group, Rh factor, direct antiglobulin test (DAT), total bilirubin, direct bilirubin, indirect bilirubin, haptoglobin, blood smear to check for spherocytosis

Laboratory data will be presented in units provided by the central laboratory.

Lab values will be summarized descriptively by visit using only values from scheduled visits.

Summaries of worst-case changes from baseline with respect to the normal range will be provided: decreases to below the normal range, changes to within the normal range or no changes from baseline and increases to above the normal range will be summarized for the worst-case post-reference visit. If a subject has a decrease to below the normal range and an increase to above the normal range during the same time interval, then the subject is counted in both the decrease to below the normal range and increase to above the normal range categories.

Separate summary tables for hematology, biochemistry, and virology laboratory tests will be produced. Changes from reference visit are produced for hematology and biochemistry only.

The denominator in percentage calculation at each scheduled visit will be based on the number of subjects with a non-missing value at each visit.

The following summaries will be provided by groups defined in Section 11:

- All laboratory values by visit
- Laboratory value changes from reference visit
- Worst-case changes from reference visit with respect to the normal range

Listings to be produced are:

- All Laboratory values, incl. changes from reference visit, values outside normal range will be flagged

11.6 Other Safety Measures

11.6.1 Vital Signs

The following summaries will be provided by groups defined in Section 11:

- Values of vital signs by scheduled visit
- Change from reference visit by scheduled visit

11.6.2 Electrocardiograms (ECG)

Shift tables will be presented by groups defined in Section 11. They will give the n (%) of subjects who shift from Screening to Week 53 among the following categories:

- Normal
- Abnormal

11.6.3 Physical Examination

At Screening, all clinically significant abnormal findings are reported on the Medical History form. For all other visits, all new clinically significant abnormal findings or clinically significant deteriorations are reported on the Adverse Events form.

11.6.4 Hemolysis

Clinical hemolysis will be considered based on criteria given in Section 8 of the Clinical Study Protocol as:

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

Hemoglobinuria, hemoglobinemia and hepatosplenomegaly will be assessed by medical review, if no clinical signs occur these criteria will be disregarded.

Hemolysis findings will be analyzed descriptively, displaying number of subjects and percentage.

11.6.5 Wells' Criteria Score

Data for Wells' criteria Score for deep vein thrombosis (DVT) and pulmonary embolism (PE) will be analyzed descriptively.

12 Pharmacokinetic Analyses

Serum samples for IgG level determination will be collected at Screening and at specified study visits.

Additional blood samples for rich PK sampling of IgG levels will be collected at Week 37 on up to 10 Japanese subjects and 30 non-Japanese subjects.

All non-compartmental analyses are to be performed according to PK-GDL-01.

The merge of PK concentration data and eCRF data to generate a data set with actual blood sampling times, actual sampling time relative to the start of the dose infusion, actual infusion durations, actual dose and PK concentrations, along with derivation of PK parameters will be performed after database lock by CSL Behring or their designate.

12.1 Drug Concentration Measures

IgG concentrations from rich PK sampling will be listed for individual subjects and summarized by nominal (planned) time points and by region (Japan vs non-Japan). 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 on both log-linear and linear scales. Mean profiles will be provided overall and stratified by dosing regimen (1, 2, 3, or

4-day administration) at Week 37 (ie, week of rich PK sampling) and region (Japan vs non-Japan).

Serum IgG levels other than the rich PK sampling will be summarized by visit, treatment sequence, period, and region (Japan vs non-Japan), separately from the rich PK summaries.

12.2 Deriving and Summarizing Pharmacokinetic Parameters

Non-compartmental PK analysis will be performed by CSL Behring or its designate for PK parameter derivation using Phoenix WinNonlin, Version 6.3 or higher. Only concentrations from rich PK sampling will be used to calculate the PK parameters based on the PK analysis set. The following PK parameters will be derived using actual sampling collection times:

$AUC_{0\text{-}tau}$	Area Under the serum concentration-time Curve from time-point zero (Day 1) through tau=Day 7 (at Week 37), calculated using a combined linear and logarithmic trapezoidal rule (linear up-log down).
C_{trough}	Trough concentration in serum, collected prior to the next infusion during a treatment regimen.
C_{max}	Maximum observed concentration in serum.
T_{max}	Time to reach C_{max}
Cl_{ss}/F	Apparent clearance at steady state
$V_{Z,SS}/F$	Apparent volume of distribution of the terminal phase at steady state

The plasma PK parameters will be listed and summarized with the following: n, mean, SD, geometric mean, geometric % CV, median, first quartile, third quartile, minimum, and maximum for all PK parameters except t_{max}. T_{max} will be summarized with n, minimum, median, first quartile, third quartile and maximum. Summary statistics will be grouped by dosing regimen (1, 2, 3, or 4-day administration) and region (Japan vs. non-Japan).

12.3 Pharmacokinetics Statistical Analyses

No statistical analysis except the summary statistics described above will be performed.

13 References

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14 Appendices

14.1 Simulation Report for Sample Size Estimation

This report is to describe the details of the simulation performed for the sample size estimation in the IgPro20_3007 study, including assumptions and scenarios, as well as the simulation code.

14.1.1 Primary Endpoint

The derivation of the primary endpoint takes into account of the following information:

- TIS assessments at the three visits Week 17, 21, and 25
- Withdrawn from IMP or study or receiving oral rescue corticosteroid treatment.

It is expected that the TIS assessments at the three visits are correlated. In addition, once a subject is withdrawn from IMP or study, or receiving oral rescue corticosteroid treatment, the subject is considered not showing response at that visit and at all subsequent visits. Therefore, the probability for a subject showing response (TIS ≥ 20 points) at one visit is conditional on the response status of the subject (including TIS, withdrawn from IMP or study, receiving oral rescue corticosteroid treatment) at the previous visit.

14.1.2 Assumptions

The assumptions used in the simulation are tabulated in Table 3 in the SAP Section 4.5. With the probability of having a TIS ≥ 20 points being specified, the probability of showing no response, including TIS < 20 points, or withdrawn from IMP or study, or receive oral rescue corticosteroid treatment, is the complement. For example, it is assumed that the probability of having a TIS ≥ 20 points at Week 17 is 65% in Treatment Sequence A, then the probability of having TIS < 20 points at Week 17 in Treatment Sequence A, being withdrawn from IMP or study, receive oral rescue corticosteroid treatment combined, is 35%.

14.1.3 Scenario

The total sample size investigated cover the range of (116, 130) and the conditional probability of having a TIS ≥ 20 points given the subject showing response at the previous visit in the range of (0.85, 0.95). Each scenario investigated was simulated 5000 times.

Table 14: Results of Sample Size Simulation

Total sample size	Probability of TIS ≥ 20 conditional on showing a response at the previous visit	Power	Estimated median responder rate in Treatment Sequence A	Estimated median responder rate in Treatment Sequence B
116	0.95	0.914	0.655	0.345
	0.9	0.855	0.603	0.310
	0.85	0.784	0.552	0.276
118	0.95	0.925	0.661	0.339
	0.9	0.869	0.610	0.305
	0.85	0.806	0.542	0.271
120	0.95	0.933	0.667	0.333
	0.9	0.878	0.600	0.300
	0.85	0.817	0.550	0.283
122	0.95	0.932	0.656	0.344
	0.9	0.882	0.607	0.311
	0.85	0.821	0.557	0.279
124	0.95	0.939	0.661	0.339
	0.9	0.895	0.597	0.306
	0.85	0.833	0.548	0.274
126	0.95	0.948	0.667	0.333
	0.9	**0.905**	**0.603**	**0.317**
	0.85	0.839	0.556	0.286
128	0.95	0.934	0.656	0.344
	0.9	0.887	0.609	0.313
	0.85	0.844	0.547	0.281
130	0.95	0.940	0.662	0.338
	0.9	0.897	0.600	0.308
	0.85	0.847	0.554	0.277

The total sample size of 126 subjects is selected as the minimum sample size for a power of ≥ 90% based on the above assumptions.

14.1.4 Simulation code (in R, version 3.4.2)

```
library(exact2x2)
##data simulation
r_act=0.65   ##response rate at W17, active arm (treatment sequence A)
r_pbo=0.30   ##response rate at W17, placebo arm (treatment sequence B)
cond_p_nonres_act=0.2
cond_p_nonres_pbo=0.1

single_set=function(N,r_act,r_pbo,cond_p_res,cond_p_nonres_act,
cond_p_nonres_pbo) {

subj=seq(1,N)
trt=c(rep("act",times=N/2), rep("pbo", times=N/2))
wk17=c(rbinom(N/2, 1, r_act), rbinom(N/2, 1, r_pbo))
wk21_act=rbinom(N/2,1,cond_p_res)*(wk17[1:(N/2)]==1)+rbinom(N/2,1,
cond_p_nonres_act)*(wk17[1:(N/2)]==0)
wk21_pbo=rbinom(N/2,1,cond_p_res)*(wk17[(N/2+1):N]==1)+rbinom(N/2,1,
cond_p_nonres_pbo)*(wk17[(N/2+1):N]==0)
wk21=c(wk21_act, wk21_pbo)
wk25_act=rbinom(N/2,1,cond_p_res)*(wk21[1:(N/2)]==1)+rbinom(N/2,1,
cond_p_nonres_act)*(wk21[1:(N/2)]==0)
wk25_pbo=rbinom(N/2,1,cond_p_res)*(wk21[(N/2+1):N]==1)+rbinom(N/2,1,
cond_p_nonres_pbo)*(wk21[(N/2+1):N]==0)
wk25=c(wk25_act, wk25_pbo)

responses=wk17+wk21
responder=(responses>0)*(wk25>0)+0

nres_act=sum(responder[1:(N/2)])
nres_pbo=sum(responder[(1+N/2):N])
tbl=matrix(c(nres_act, N/2-nres_act, nres_pbo, N/2-nres_pbo), 2, 2)
return(c(fisher.test(tbl,    alternative="greater")$p.value,    2*nres_act/N,
2*nres_pbo/N))
}

N_RANGE=rep(seq(116, 130, by=2), each=3)
PROB_CON=rep(c(0.95, 0.9, 0.85), 8)
power=rep(-1, 24)
median_rate_a=rep(-1, 24)
median_rate_p=rep(-1, 24)

ALL=cbind(N_RANGE, PROB_CON, power, median_rate_a, median_rate_p)
for (k in 1:24){
   N=ALL[k,1]
   cond_p_res=ALL[k,2]
   set.seed(12345)
   result=matrix(-1,ncol=3,nrow=5000)

     for (i in 1:nrow(result))
```

```
{result[i,]=single_set(N,r_act,r_pbo,cond_p_res,cond_p_nonres_act,cond_p_nonr
es_pbo)}

   ALL[k, 3]=sum(result[,1]<0.025)/nrow(result)  ##power 85.54%
   ALL[k, 4]=median(result[,2])  ##median of responder rate in active arm
   ALL[k, 5]=median(result[,3])  ##median of responder rate in pbo arm
}

ALL

write.csv(ALL,  "H:/Projects/IgPro20_3007/Stats  Technical/Sample  Size/Design
Dec2018/all.csv")
```

The results have been re-programmed independently in SAS (version 9.4) which confirmed the power calculation with less than 1.2% difference.

Signature Page

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