

Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Phase IIa, Randomized, Parallel, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Enpatoran in Dermatomyositis and Polymyositis Participants receiving Standard of Care
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Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
5.0	Global Amendment 4	24 June 2024
4.0	Global Amendment 3	02 August 2023
3.0	Global Amendment 2	03 April 2023
2.0	Global Amendment 1	20 March 2023
1.0	Original Protocol	12 August 2022

Protocol Version 5.0 (24 June 2024)

Overall Rationale for the Amendment

The rationale for this protocol amendment is to address the potential risk of cardiac arrhythmia within this study, based on the changes requested by the US FDA, and to enable participation of patients impacted by this change.

Section # and Name	Description of Change	Brief Rationale
1.3.1 Double-Blind Placebo Controlled Treatment Period (Table 1) 1.3.2 Open label Extension Period (Table 2)	Added text "corrected using Fridericia's formula" for ECG." Line regarding Study Intervention updated.	To provide more clarity on the participant population description. Alignment with the text in the notes.
1.3.1 Double-Blind Placebo Controlled Treatment Period (Table 1), 1.3.2 Open label Extension Period (Table 2) 3 Objectives and Estimands 8.2.4 Clinical Safety Laboratory Assessments, CCI	Immune cell subset analysis has been removed from protocol	Questionable sample and resulting data integrity, due to sample acquisition out of acceptable stability window.
2.3.1 Risk Assessment 5.2 Exclusion Criteria	- Changed asymptomatic QTcF at baseline from ≥ 500 ms to ≥ 450 ms for male participants, and ≥ 470 ms for female participants. - Added exclusion of participants with a family history of sudden cardiac death, unexplained death, long QT syndrome, or death from a primary dysrhythmia potentially associated with QT prolongation in any family member. - Added exclusion of participants with clinically abnormal electrolytes during Screening that cannot be corrected.	To address cardiac arrhythmia potential risk and provide more clarity of the participant population description.

Section # and Name	Description of Change	Brief Rationale
CCI [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]	[REDACTED]
Section 8.2.3 Electrocardiograms	Addition of language regarding potential review of ECG tracings.	Allow flexibility.
Section 8.3.8 Management of Adverse Events (Including AESI)	Changed QT to QTcF for cardiac signs and symptoms.	To provide more clarity on the cardiac signs and symptoms to be considered for management of AEs and AESIs.
Appendix 2 Study Governance	Addition of language regarding the applicable EU legislation.	Preparation of CTIS transition.
Appendix 5 Clinical Laboratory Tests	Added RBC count and reticulocytes (absolute count). Footnote on ESR rephrased.	Omission in earlier versions. To provide more clarity.
Appendix 6 Myositis Medication Guidance (Table 6)	Added washout time for immunomodulators and/or immunosuppressants.	To provide more clarity on the medications with required duration of stable dose.
Throughout	Minor editorial and document formatting revisions.	Administrative and editorial updates.

AE = adverse event(s), AESI = adverse events of special interest(s), ECG = electrocardiogram, QTcF= QT corrected for heart rate by Fridericia's cube root formula; RBC = red blood cell.

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Table of Contents

Title Page	1
Table of Contents	5
Table of Tables	8
Tables of Figures	9
1 Protocol Summary	10
1.1 Synopsis	10
1.2 Schema	16
1.3 Schedule of Activities	17
1.3.1 Double-Blind Placebo Controlled Treatment Period	17
1.3.2 Open Label Extension Period	26
2 Introduction	30
2.1 Study Rationale	30
2.2 Background	30
2.3 Benefit/Risk Assessment	31
2.3.1 Risk Assessment	33
2.3.2 Risk Assessment in the Context of SARS-CoV-2	37
2.3.3 COVID-19 Vaccination	37
2.3.4 Benefit Assessment	37
2.3.5 Overall Benefit: Risk Conclusion	38
3 Objectives and Estimands	38
4 Study Design	43
4.1 Overall Design	43
4.2 Scientific Rationale for Study Design	44
4.3 Justification for Dose	45
4.4 End of Study Definition	45
5 Study Population	46
5.1 Inclusion Criteria	46
5.1.1 Inclusion Criteria for Entry into Open Label Extension	50
5.2 Exclusion Criteria	51
5.2.1 Exclusion Criteria for Open Label Extension Period	59
5.3 Lifestyle Considerations	60

5.3.1	Meals and Dietary Restrictions.....	60
5.3.2	Activity	60
5.4	Screen Failures.....	60
5.5	Criteria for Temporarily Delaying the Enrollment/Randomization/Administration of Study Intervention Administration	61
6	Study Intervention(s) and Concomitant Therapies	61
6.1	Study Intervention(s) Administration	61
6.2	Study Intervention(s) Preparation, Handling, Storage, and Accountability.....	62
6.3	Measures to Minimize Bias: Study Intervention Assignment and Blinding	63
6.3.1	Study Intervention Assignment	63
6.3.2	Blinding	64
6.3.3	Emergency Unblinding.....	65
6.4	Study Intervention Compliance	65
6.5	Dose Modification	66
6.6	Continued Access to Study Intervention after the End of the Study ..	66
6.7	Treatment of Overdose	66
6.8	Concomitant Therapy	66
6.8.1	Corticosteroids	66
6.8.1.1	Corticosteroid Tapering	66
6.8.1.2	Corticosteroid Rescue Medicine.....	67
6.8.2	Permitted Medicines	67
6.8.3	Prohibited Medicines	69
6.8.4	Other Interventions	71
7	Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal.....	71
7.1	Discontinuation of Study Intervention.....	71
7.1.1	Temporary Discontinuation	73
7.2	Participant Discontinuation/Withdrawal from the Study	73
7.3	Lost to Follow-Up.....	73
8	Study Assessments and Procedures	74
8.1	Efficacy Assessments and Procedures	75

8.2	Safety Assessments and Procedures	75
8.2.1	Physical Examinations	75
8.2.2	Vital Signs	76
8.2.3	Electrocardiograms	76
8.2.4	Clinical Safety Laboratory Assessments	76
8.2.5	Suicidal Ideation and Behavior Risk Monitoring	77
8.2.6	Spirometry or DLCO	78
8.3	Adverse Events, Serious Adverse Events, and Other Safety Reporting	78
8.3.1	Method of Detecting Adverse Events and Serious Adverse Events...	79
8.3.2	Follow-up of Adverse Events and Serious Adverse Events	79
8.3.3	Regulatory Reporting Requirements for Serious Adverse Events	79
8.3.4	Pregnancy	80
8.3.5	Cardiovascular and Death Events	81
8.3.6	Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs	81
8.3.7	Adverse Events of Special Interest	81
8.3.8	Management of Adverse Events (Including AESI)	81
8.4	Pharmacokinetics	83
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CCI		
8.7	Immunogenicity Assessments	85
8.8	Health Economics	85
9	Statistical Considerations	85
9.1	Statistical Hypotheses	85
9.2	Sample Size Determination	85
9.3	Analyses Sets	86
9.4	Statistical Analyses	87
9.4.1	Efficacy Analyses	87
9.4.2	Safety Analyses	88
9.4.3	Other Analyses	88
9.4.4	Sequence of Analyses	88
10	References	90

11	Appendices	93
Appendix 1	Abbreviations.....	93
Appendix 2	Study Governance.....	96
Appendix 3	Contraception and Barrier Requirements	102
Appendix 4	Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.....	104
Appendix 5	Clinical Laboratory Tests	110
Appendix 6	Myositis Medication Guidance.....	112
Appendix 7	Corticosteroids Guidance.....	115
Appendix 8	Efficacy and Patient-Reported Outcome Assessments and Procedures.....	119
Appendix 9	Autoantibody Status.....	125
CCI		
Appendix 11	Protocol Amendment History	127
Appendix 12	Sponsor Signature Page	130
Appendix 13	Coordinating Investigator Signature Page	131
Appendix 14	Principal Investigator Signature Page.....	132

Table of Tables

Table 1	Schedule of Assessments for DBPC Treatment Period	17
Table 2	Schedule of Assessments for Optional OLE Period	26
Table 3	Potential Risks of Clinical Significance	33
Table 4	Conditional Probability to Detect Treatment Effect in Total Improvement Score at Week 24	86
Table 5	Prohibited Medications With Required Washout	112
Table 6	Medications with Required Duration of Stable Dose	114
Table 7	Corticosteroid Guidance for the Screening Period and 24-Week DBPC Period	115
Table 8	Corticosteroid Guidance for the Open Label Extension Period	116
Table 9	Prednisone-equivalence Calculation (Total Daily Dose)	118
Table 10	IMACS Core Set Measures	122

Tables of Figures

Figure 1	Study Schema	16
Figure 2	Examples of Corticosteroid Tapering Schedules.....	117

1 Protocol Summary

1.1 Synopsis

Protocol Title: A Phase IIa, Randomized, Parallel, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Enpatoran in Dermatomyositis and Polymyositis Participants receiving Standard of Care

Short Title: Phase IIa Study of Enpatoran in Dermatomyositis (DM) and Polymyositis (PM)

Rationale: The purpose of this study is to evaluate the efficacy and safety of orally administered enpatoran in idiopathic inflammatory myopathies, specifically DM and PM patients in a randomized, double-blind, placebo-controlled (DBPC) 24-week study.

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Objectives and Estimands:

Objectives	Estimands	Ref. #
Primary		
To evaluate the effect of enpatoran compared to placebo on the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Total Improvement Score (TIS) at Week 24 of the DBPC period in DM and PM participants	Endpoint: ACR/EULAR mean TIS at Week 24, a weighted composite endpoint (range 0 to 100) derived from the absolute % improvement from baseline in the International Myositis Assessment and Clinical Studies (IMACS) Core Set Measures (CSM): - Physician Global Activity (PGA) Visual Analogue Scale (VAS) derived from Myositis Disease Activity Assessment Tool (MDAAT) - Patient Global Activity (PtGA) VAS - Manual Muscle Testing (MMT)-8 - Health Assessment Questionnaire-Disability Index (HAQ-DI) - Most abnormal muscle-associated enzymes - Extramuscular Activity Assessment derived from MDAAT	1
	Population: DM and PM patients Treatment: Enpatoran compared to placebo CCI Population-Level Summary: difference of means and 95% confidence intervals	
To evaluate the safety and tolerability of enpatoran in DM and PM participants during the DBPC period	Endpoints: - Occurrence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and adverse events of special interest (AESIs) during the DBPC period - Changes in laboratory parameters - Change in vital signs - Change in 12-lead electrocardiogram (ECG)	2
	Population: DM and PM patients Treatment: Enpatoran compared to placebo Intercurrent Event Strategy: treatment policy Population-Level Summary: Descriptive statistics	

Objectives	Estimands	Ref. #
Secondary		
To evaluate the efficacy in disease control with enpatoran compared to placebo in DM and PM participants during the DBPC period	Endpoints: TIS Responder: • Occurrence of TIS ≥ 20 at Week 16, TIS ≥ 20 at Week 24 • Occurrence of TIS ≥ 40 at Week 16, TIS ≥ 40 at Week 24 • Occurrence of TIS ≥ 60 at Week 16, TIS ≥ 60 at Week 24 Population: DM and PM patients Treatment: Enpatoran compared to placebo CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] Population-Level Summary: number and % of participants with TIS ≥ 20, ≥ 40 or ≥ 60; differences to placebo with 95% confidence interval (CI); a participant is defined as responder if having a TIS score of ≥ 20 points and not having met any of the intercurrent events.	3
	Endpoints: • TIS at each visit from Week 4 up to and including Week 24 • PGA as derived from MDAAT at each visit from Week 4, up to and including Week 24 • PtGA at each visit from Week 4, up to and including Week 24 • Extramuscular Activity Assessment derived from MDAAT at each visit from Week 4, up to and including Week 24 • MMT-8 at each visit from Week 4, up to and including Week 24 • HAQ-DI at each visit from Week 4, up to and including Week 24 • Percent change from baseline in most abnormal muscle enzyme at each visit from Week 4, up to and including Week 24 • Absolute and % change for all above components	4

Objectives	Estimands	Ref. #
	Population: DM and PM patients Treatment: Enpatoran compared to placebo CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] Population-Level Summary: Difference of means and 95% CI	
	Endpoint: IMACS Responder, defined by the IMACS group Definition of Improvement (DOI) at Week 16 and at Week 24 as defined by: 3 of any 6 IMACS CSMs improved by $\geq 20\%$, with no more than 2 IMACS CSMs worse by $\geq 25\%$ (which cannot be MMT-8)	5
	Population: DM and PM patients Treatment: Enpatoran compared to placebo CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] Population Level Summary: Number and % of responders; difference from placebo with 95%CI	

Objectives	Estimands	Ref. #
To evaluate the efficacy on cutaneous disease activity of DM (in DM participants and PM participants with rash, defined as Cutaneous Dermatomyositis Disease Area and Severity Index [CDASI]-A ≥ 7) with enpatoran compared to placebo during the DBPC period	Endpoints: - Change and percent change from baseline in CDASI-A and CDASI-D at each visit from Week 4, up to Week 24 - Change and percent change from baseline in Investigator's Global Assessment (IGA) skin activity at each visit from Week 4, up to Week 24 Population: DM patients and PM patients with rash Treatment: Enpatoran compared to placebo CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] Population Level Summary: difference of means and confidence intervals	6
To evaluate the safety and tolerability of enpatoran in DM and PM participants during the Open Label Extension (OLE) period (according to treatment received during DBPC)	Endpoints: - Occurrence of TEAEs, SAEs and AESI during OLE period - Changes in laboratory parameters - Change in vital signs - Change in 12-lead ECG Population: DM and PM patients Treatment: Enpatoran compared to placebo Intercurrent Event Strategy: treatment policy Population-Level Summary: Descriptive statistics	7

Overall Design: This is a Phase IIa, randomized, parallel, double-blind, placebo-controlled study in participants with active DM and PM treated with standard of care to evaluate the efficacy and safety of enpatoran administered orally twice per day for 24 weeks.

Brief Summary:

The purpose of this study is to evaluate the efficacy and safety of orally administered enpatoran tablets in DM and PM patients compared to placebo over 24 weeks in a randomized, double-blind, parallel study. This study offers an optional OLE period for completers of the 24-week double-blind treatment period. Study details include:

- Study Duration: 31 weeks (5-week Screening period + 24 weeks double-blind treatment period + 2 weeks Safety Follow-up). Optional OLE period: 26 weeks (24-week treatment period + 2 weeks Safety Follow-up).
- Treatment Duration: at least 24 weeks (double-blind treatment period) + optional 24-week OLE treatment period.
- Visit Frequency: every 4 weeks
- Enpatoran is not available through an expanded access program.

Number of Participants: Approximately 40 participants will be randomly assigned in a 1:1 ratio to study intervention. Participants will be stratified according to disease subtype at Screening (DM or PM as per 2017 ACR/EULAR classification criteria). Balanced inclusion of DM and PM patients will be managed by Interactive Response Technology, targeting between 40% and 60% of patients with DM or PM. The assumption is that no more than 5% of participants will drop out.

Study Intervention Groups and Duration:

The planned total duration of the study is up to 31 weeks: (up to) 5-week Screening period, 24-week DBPC treatment period followed by a 2-week Safety Follow-up period. This Safety Follow-up period is not required for participants who enroll in the OLE period at Week 24.

Upon completion of 24-week DBPC treatment period, signature of informed consent, and confirmation of eligibility, the participant will be enrolled and allocated to optional OLE period: 26 weeks (24-week treatment period followed by a 2-week Safety Follow-up period).

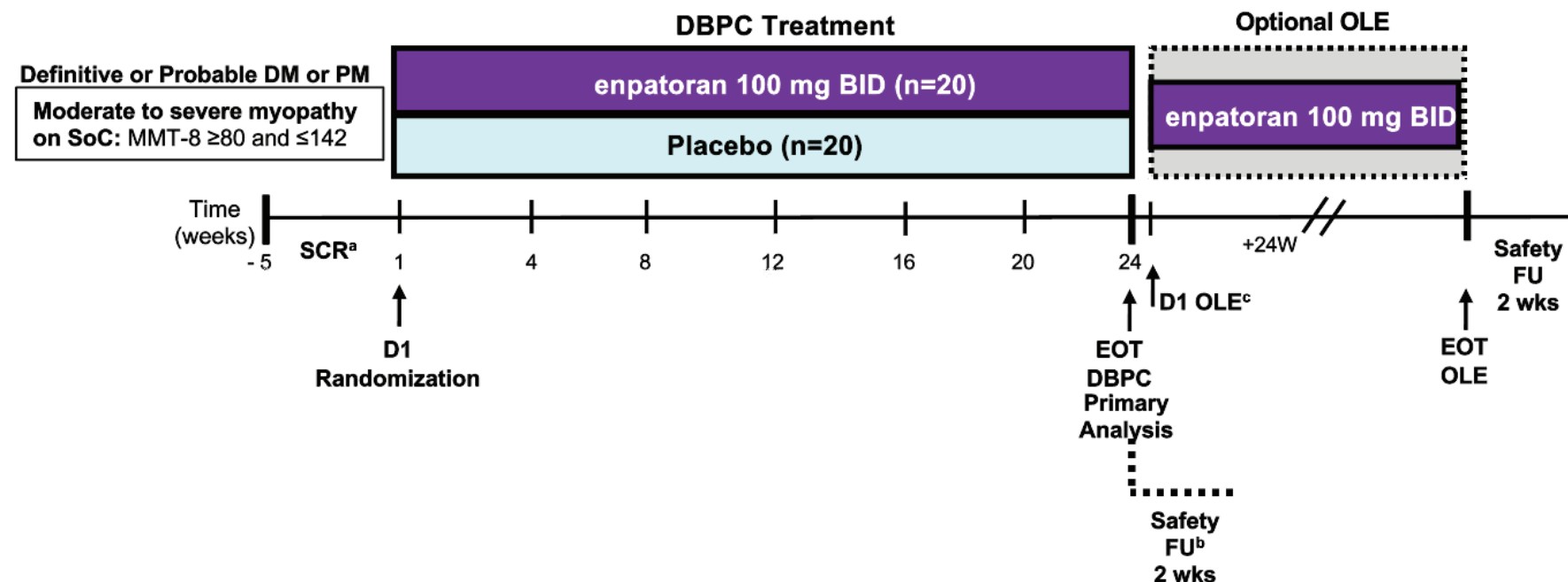
The optional OLE treatment Period will provide data on long-term exposure and allow all completers of the DBPC period with the option to receive active enpatoran treatment. Only completers of the 24-week DBPC treatment period are eligible for the OLE period in order not to encourage early termination in the DBPC period. For countries in which Authorities (local IRB/IEC or local Health Authorities) require submission of additional supporting information prior to start of OLE period, participation in the OLE period will only be offered after approval is received from the above Authorities.

Involvement of Special Committee(s): Yes

Special oversight committees will include Independent Data Monitoring Committee, Study Steering Committee, idiopathic inflammatory myopathies expert committee, and Firewall team. The Firewall team will be composed of a restricted group of individuals within the Sponsor team who are not directly involved in the study conduct activities.

1.2 Schema

Figure 1 Study Schema



Participants who complete the 24-week DBPC treatment period will be offered participation in the 24-week OLE treatment period of the study (upon eligibility fulfillment and signed consent). The enpatoran dose during the OLE period may be modified based on emerging clinical safety data, without exceeding the highest clinically investigated enpatoran dose.

BID=twice daily, D=Day, DBPC=double-blind placebo-controlled, DM=dermatomyositis, EOT=End of Treatment, FU=Follow-up, MMT-8=Manual Muscle Testing, OLE=Open Label Extension, PM=polymyositis, SCR=Screening, SoC=Standard of Care, W=Week, wks=weeks.

a Screening up to 5 weeks.

b Safety FU visit for participants not entering the OLE. Safety FU period is not required for participants who enroll in the OLE period within < 7 days of W24 (phone visit required if OLE D1 visit is 7 to 14 days after W24).

c If within the 3-day window of the DBPC W24/EOT visit, participants might only complete the DBPC W24/EOT or OLE D1 (preferred option). If beyond this window, participants must attend both visits (DBPC W24/EOT and OLE D1).

1.3 Schedule of Activities

1.3.1 Double-Blind Placebo Controlled Treatment Period

Table 1 Schedule of Assessments for DBPC Treatment Period

	SCR	DBPC Treatment Period								Safety Follow-up ^a		Notes
Assessments and Procedures (Weeks)		0	4	8	12	16	20	24/ EOT	ET ^b	25 ☎	26	
Study Day	-35 to -1	1	29	57	85	113	141	169	-	176	183	
Visit Window (Days)			± 5	± 5	± 5	± 5	± 5	± 3	+ 3	+ 3	+ 3	
Screening and Randomization only Assessments												
Informed consent	X											
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OLE consent	X											
Inclusion/exclusion criteria	X	X										Recheck clinical status, CDASI-A, MMT-8, PtGA, PGA and Extramuscular Activity Assessment (as part of MDAAT), and HAQ-DI score prior to randomization (see Exclusion Criterion 28).
Eligibility packet	X											Submission as soon as possible after the Screening Visit. See Section 5.
Demographics	X											

	SCR	DBPC Treatment Period								Safety Follow-up ^a		Notes
Assessments and Procedures (Weeks)		0	4	8	12	16	20	24/ EOT	ET ^b	25 ☎	26	
Study Day	-35 to -1	1	29	57	85	113	141	169	-	176	183	
Visit Window (Days)			± 5	± 5	± 5	± 5	± 5	± 3	+ 3	+ 3	+ 3	
Past and current medical conditions, medications	X											History of alcohol or drug abuse. Medication history for the treatment of disease; other study-relevant medication history within 12 months prior to Screening Visit (see Section 6.8).
Autoantibody status	X											Autoantibody status (see Appendix 5 and Appendix 9). Historical data are also acceptable.
Documentation of DM or PM with moderate to severe myopathy	X											Includes diagnosis of probable or definitive DM or PM as per 2017 ACR/EULAR classification criteria, disease activity and disease severity criteria (see Inclusion Criterion 2).
Chest imaging	X											All patients: Required at Screening unless performed within past 6 month, PLUS at any visit where there are new or significantly worsening clinical symptoms (pulmonary). Chest images (CXR, CT, or MRI) to be stored as source documents in the participant file.
Serum virology	X											Hepatitis B and C screening, HIV. See Exclusion Criterion 10 and Appendix 5.
TB assessment	X											See Exclusion Criterion 11 and Appendix 5.

	SCR	DBPC Treatment Period								Safety Follow-up ^a		Notes
Assessments and Procedures (Weeks)		0	4	8	12	16	20	24/ EOT	ET ^b	25 ☎	26	^a Safety FU visits by phone and at site at 7 and 14 days, respectively, after ET or W24/EOT visit. Not required for participants who have OLE D1 visit within <7 days of W24 (phone visit required if OLE D1 visit is 7 to 14 days after W24). ^b ET visit should occur as soon as possible after premature discontinuation and replaces EOT visit.
Study Day	-35 to -1	1	29	57	85	113	141	169	-	176	183	
Visit Window (Days)			± 5	± 5	± 5	± 5	± 5	± 3	+ 3	+ 3	+ 3	
Randomization												
Randomization		X										Randomization occurs on Day 1, after confirmation of eligibility and prior to start of study intervention.
Patient Reported Outcomes (should be completed before other assessments)												
PtGA	X	X	X	X	X	X	X	X	X			See Appendix 8 .
HAQ-DI	X	X	X	X	X	X	X	X	X			See Appendix 8 .
CCI												
Patient experience in-trial interviews								X	X			Selected sites. Within 2 weeks of the EOT/ET visit. See Appendix 8 .
Clinical Assessments and Study Intervention												
Study intervention		←-----→										Twice per day administration with water (200 mL) and no food restrictions. On study visit days, the participant will be asked not to self-administer study intervention at home and hold the dose until predose assessments have been completed in the clinic. See Section 6.1. Administration up to but not including EOT/ET Visit.

	SCR	DBPC Treatment Period								Safety Follow-up ^a		Notes
Assessments and Procedures (Weeks)		0	4	8	12	16	20	24/ EOT	ET ^b	25 ☎	26	^a Safety FU visits by phone and at site at 7 and 14 days, respectively, after ET or W24/EOT visit. Not required for participants who have OLE D1 visit within <7 days of W24 (phone visit required if OLE D1 visit is 7 to 14 days after W24). ^b ET visit should occur as soon as possible after premature discontinuation and replaces EOT visit.
Study Day	-35 to -1	1	29	57	85	113	141	169	-	176	183	
Visit Window (Days)			± 5	± 5	± 5	± 5	± 5	± 3	+ 3	+ 3	+ 3	
Exposure data documentation		←-----→										Participants to record date, time, kit number and amount of study intervention administration and whether a meal was consumed within 1 h predose or 2 h postdose in the paper diary card or mobile application provided. See Section 6.2.
Study intervention accountability		←-----→										See Section 6.2.
Mealtime documentation		X	X	X	X	X	X	X				On scheduled study visit days with PK assessment, record the date and time of the closest meal before and after the study intervention administration. See Section 5.3.1.
Adverse event review	←-----→											Continuous throughout study. Participants to capture symptoms in diary card or phone application.
Concomitant therapy review	←-----→											
Exercise regimen	X	X	X	X	X	X	X	X	X			Documentation of any exercise program. See Section 6.8.4.
Vital signs	X	X	X	X	X	X	X	X	X		X	Height collected at Screening Visit only. BMI determined at Screening and EOT visit only. Obtain vital signs before any scheduled ECG. See Section 8.2.2.

	SCR	DBPC Treatment Period								Safety Follow-up ^a		Notes
Assessments and Procedures (Weeks)		0	4	8	12	16	20	24/ EOT	ET ^b	25 ☎	26	
Study Day	-35 to -1	1	29	57	85	113	141	169	-	176	183	
Visit Window (Days)			± 5	± 5	± 5	± 5	± 5	± 3	+ 3	+ 3	+ 3	
ECG	X	X	X	X		X		X	X		X	D1: predose (as Baseline) and 1-2 h postdose. All other days: 1-2 h postdose. All patients: Required at Screening, D1, W4, W8, W16, W24/EOT or ET PLUS at any visit where there are new or significantly worsening clinical symptoms (cardiac) Patients with an abnormal finding when compared to D1: all the above PLUS W26. Corrected using Fridericia's formula. See Section 8.2.3.
Physical examination	X	X	X	X	X	X	X	X	X		X	Including routine neurological examination
C-SSRS	X							X	X			See Appendix 8 and Section 8.2.5.
CDASI	X	X	X	X	X	X	X	X	X			DM participants and PM participants with rash at Screening. See Appendix 8 .
IGA skin activity	X	X	X	X	X	X	X	X	X			DM participants and PM participants with rash at Screening. See Appendix 8 .
MMT-8	X	X	X	X	X	X	X	X	X			See Appendix 8 .

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	SCR	DBPC Treatment Period								Safety Follow-up ^a		Notes
Assessments and Procedures (Weeks)		0	4	8	12	16	20	24/ EOT	ET ^b	25 ☎	26	^a Safety FU visits by phone and at site at 7 and 14 days, respectively, after ET or W24/EOT visit. Not required for participants who have OLE D1 visit within <7 days of W24 (phone visit required if OLE D1 visit is 7 to 14 days after W24). ^b ET visit should occur as soon as possible after premature discontinuation and replaces EOT visit.
Study Day	-35 to -1	1	29	57	85	113	141	169	-	176	183	
Visit Window (Days)			± 5	± 5	± 5	± 5	± 5	± 3	+ 3	+ 3	+ 3	
MDAAT	X	X	X	X	X	X	X	X	X			Includes constitutional, cutaneous, joints, gastrointestinal, pulmonary (CXR/HRCT, spirometry, or DLCO if required; test results to be recorded; not to be repeated if already performed as part of safety assessments), cardiovascular (ECG if required; not to be repeated if already performed as part of safety assessments) and myositis components. See Appendix 8 .
Spirometry or DLCO	X ^c	X						X	X		X	See Section 8.2.6. ^c Spirometry mandatory for Screening (see Exclusion Criterion 4). All patients: Required at Screening, D1, W24/EOT or ET PLUS at any visit where there are new or significantly worsening clinical symptoms (pulmonary). Patients with an abnormal finding when compared to D1: all the above PLUS W26.
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CCI												

	SCR	DBPC Treatment Period								Safety Follow-up ^a		Notes
Assessments and Procedures (Weeks)		0	4	8	12	16	20	24/ EOT	ET ^b	25 ☎	26	
Study Day	-35 to -1	1	29	57	85	113	141	169	-	176	183	
Visit Window (Days)			± 5	± 5	± 5	± 5	± 5	± 3	+ 3	+ 3	+ 3	
Clinical Safety Laboratory Assessments												
Urine pregnancy test/ Serum pregnancy test	X	X	X	X	X	X	X	X	X			WOCBP only (see Inclusion Criterion 7). Negative serum or highly sensitive urine pregnancy test is required at Screening and within 24 h before the first dose of study intervention. Highly sensitive urine pregnancy test at each visit or a serum test if required by local regulation or the IRB/IEC (see Appendix 5).
FSH and estradiol	X											Morning sample. For non-WOCBP only to determine postmenopausal status.
CCI												
Reflex testing for HBV DNA	X	X			X			X	X			Only for participants who entered the study with negative HBV surface antigen and positive for anti-HBV surface Ab and/or anti-HBV core Ab with no detectable HBV DNA at Screening. See Section 8.2.4 and Appendix 5.
Routine urinalysis		X						X	X			See Appendix 5. Samples can be collected pre or postdose.
Routine hematology, biochemistry	X	X	X	X	X	X	X	X	X		X	See Appendix 5. Samples collected predose.

	SCR	DBPC Treatment Period								Safety Follow-up ^a		Notes
Assessments and Procedures (Weeks)		0	4	8	12	16	20	24/ EOT	ET ^b	25 ☎	26	^a Safety FU visits by phone and at site at 7 and 14 days, respectively, after ET or W24/EOT visit. Not required for participants who have OLE D1 visit within <7 days of W24 (phone visit required if OLE D1 visit is 7 to 14 days after W24). ^b ET visit should occur as soon as possible after premature discontinuation and replaces EOT visit.
Study Day	-35 to -1	1	29	57	85	113	141	169	-	176	183	
Visit Window (Days)			± 5	± 5	± 5	± 5	± 5	± 3	+ 3	+ 3	+ 3	
Muscle-associated enzymes	X	X	X	X	X	X	X	X	X		X	See Appendix 5 . Samples collected predose (as part of routine biochemistry).
Pharmacokinetic and Pharmacodynamic Assessments												
Predose PK		X	X	X	X							PK blood collection must be done within 60 min prior to the morning dose administration. Morning dose of study intervention to be administered after PK blood collection. See Section 8.4 .
Postdose PK		X	X	X		X	X	X				D1 and W4: Blood collected 1-2 h postdose and 4-6 h postdose (last assessment before participant leaves). W8: Blood collected 1-2 h postdose. W16, W20 and W24: Blood collected any time of the visit. See Section 8.4 .
CCI												
CCI												
CCI												

	SCR	DBPC Treatment Period								Safety Follow-up ^a		Notes
Assessments and Procedures (Weeks)		0	4	8	12	16	20	24/ EOT	ET ^b	25 ☎	26	^a Safety FU visits by phone and at site at 7 and 14 days, respectively, after ET or W24/EOT visit. Not required for participants who have OLE D1 visit within <7 days of W24 (phone visit required if OLE D1 visit is 7 to 14 days after W24). ^b ET visit should occur as soon as possible after premature discontinuation and replaces EOT visit.
Study Day	-35 to -1	1	29	57	85	113	141	169	-	176	183	
Visit Window (Days)			± 5	± 5	± 5	± 5	± 5	± 3	+ 3	+ 3	+ 3	
	■	■	■	■	■	■	■	■	■	■	■	CCI 

ACR/EULAR=American College of Rheumatology/European League Against Rheumatism, Ab=antibody, BMI=Body mass index, CDASI=Cutaneous Dermatomyositis Area and Severity Index, C-SSRS=Columbia-Suicide Severity Rating Scale, CT=computed tomography, CXR=chest X-ray, D=Day, DBPC=Double-Blind Placebo Controlled, DLCO=Diffusing capacity of the lungs for carbon monoxide, DM=dermatomyositis, ECG=electrocardiogram, EOT=End of Treatment, ET=Early Termination, CCI , FU=follow-up, h=hour, HAQ-DI=Health Assessment Questionnaire-Disability Index, HBV=Hepatitis B Virus, HIV=Human Immunodeficiency Virus, HRCT=high-resolution computed tomography, IEC=independent ethics committee, IgA=immunoglobulin A, IGA=Investigator's Global Assessment, IgG=immunoglobulin G, IgM=immunoglobulin M, IRB = institutional review board, CCI , MDAAT=Myositis Disease Activity Assessment Tool, MMT=manual muscle testing, MRI=magnetic resonance imaging, OLE=Open Label Extension, PK=pharmacokinetic, PM=polymyositis, PtGA=Patient Global Activity, SCR=Screening, CCI , TB=tuberculosis, W=Week, WOCBP=women of childbearing potential.

1.3.2 Open Label Extension Period

Table 2 Schedule of Assessments for Optional OLE Period

	OLE Treatment Period						Safety Follow-up ^c		Notes
Assessments and Procedures (Weeks)	0	4	8 ☎	12	24/ EOT	ET ^b	25 ☎	26	^a If within the window of the DBPC W24/EOT visit (W24+3 days; preferred option), participants should only complete the DBPC W24/EOT or OLE D1. If beyond this window, participants must attend both visits (DBPC W24/EOT and OLE D1). More than 2 weeks window between both visits requires prior approval from the Medical Monitor. ^b ET Study Visit should occur as soon as possible after premature discontinuation and replaces the EOT Visit. ^c Safety FU visits by phone and at site at 7 and 14 days, respectively, after ET or W24/EOT visit.
Study Day	1 ^a	29	57	85	169		176	183	
Visit Window (Days)		± 5	± 5	± 5	± 5	+ 5	+ 3	+ 3	
OLE Eligibility Assessments									
Verify participant remains eligible for the study	X								See Sections 5.1.1 and 5.2.1.
Reflex testing for HBV DNA	X			X	X	X			Additional HBV DNA PCR testing must be performed for participants who entered the study with negative HBV surface antigen and positive for anti-HBV surface Ab and/or anti-HBV core Ab with no detectable HBV DNA at Screening (DBPC Screening).
Patient Reported Outcomes (should be completed before other assessments)									
PtGA	X			X	X	X			See Appendix 8.
HAQ-DI	X			X	X	X			See Appendix 8.
Clinical Assessments and Study Intervention									
Study intervention	←-----→								Twice per day administration with water (200 mL) and no food restrictions. Administration up to but not including EOT/ET Visit. On study visit days, the participant will be asked not to self-administer study intervention at home and hold the dose until predose assessments have been completed in the clinic. See Section 6.1.

	OLE Treatment Period						Safety Follow-up ^c		Notes
Assessments and Procedures (Weeks)	0	4	8 ☎	12	24/ EOT	ET ^b	25 ☎	26	^a If within the window of the DBPC W24/EOT visit (W24+3 days; preferred option), participants should only complete the DBPC W24/EOT or OLE D1. If beyond this window, participants must attend both visits (DBPC W24/EOT and OLE D1). More than 2 weeks window between both visits requires prior approval from the Medical Monitor.
Study Day	1 ^a	29	57	85	169		176	183	
Visit Window (Days)		± 5	± 5	± 5	± 5	+ 5	+ 3	+ 3	^b ET Study Visit should occur as soon as possible after premature discontinuation and replaces the EOT Visit. ^c Safety FU visits by phone and at site at 7 and 14 days, respectively, after ET or W24/EOT visit.
Exposure data documentation	←-----→								Participants to record date, time, kit number and amount of study intervention administration and whether a meal was consumed within 1 h predose or 2 h postdose in the paper diary card or mobile application provided. See Section 6.2.
Study intervention accountability	←-----→								See Section 6.2.
Mealtime documentation	X			X	X				On scheduled study visit days with PK assessment, record the date and time of the closest meal before and after the study intervention administration. See Section 5.3.1.
Adverse event review	←-----→								Continuous throughout study. Participants to capture symptoms in diary card or phone application.
Concomitant therapy review	←-----→								
Exercise regimen	X	X	X	X	X	X			Documentation of any exercise program. See Section 6.8.4.
Vital signs	X	X		X	X	X		X	Obtain vital signs before any scheduled ECG. See Section 8.2.2.
ECG	X	X		X	X	X		X	D1: predose (as Baseline) and 1-2 h postdose. All other days: 1-2 h postdose. All patients: Required at D1, W4, W12, W24/EOT or ET PLUS at any visit where there are new or significantly worsening clinical symptoms (cardiac). Patients with an abnormal finding when compared to D1: all the above PLUS W26. Corrected using Fridericia's formula. See Section 8.2.3.
Physical examination	X	X		X	X	X		X	Including routine neurological examination.

	OLE Treatment Period						Safety Follow-up ^c		Notes
Assessments and Procedures (Weeks)	0	4	8 ☎	12	24/ EOT	ET ^b	25 ☎	26	^a If within the window of the DBPC W24/EOT visit (W24+3 days; preferred option), participants should only complete the DBPC W24/EOT or OLE D1. If beyond this window, participants must attend both visits (DBPC W24/EOT and OLE D1). More than 2 weeks window between both visits requires prior approval from the Medical Monitor.
Study Day	1 ^a	29	57	85	169		176	183	
Visit Window (Days)		± 5	± 5	± 5	± 5	+ 5	+ 3	+ 3	^b ET Study Visit should occur as soon as possible after premature discontinuation and replaces the EOT Visit. ^c Safety FU visits by phone and at site at 7 and 14 days, respectively, after ET or W24/EOT visit.
C-SSRS	X				X	X			See Appendix 8 and Section 8.2.5.
CDASI	X			X	X	X			DM participants and PM participants with rash. See Appendix 8 .
IGA skin activity	X			X	X	X			DM participants and PM participants with rash. See Appendix 8 .
MMT-8	X			X	X	X			See Appendix 8 .
CCI									
MDAAT	X			X	X	X			Includes constitutional, cutaneous, joints, gastrointestinal, pulmonary (CXR/HRCT, spirometry, or DLCO if required; test results to be recorded; not to be repeated if already performed as part of safety assessments), cardiovascular (ECG if required; not to be repeated if already performed as part of safety assessments) and myositis components. See Appendix 8 .
Spirometry or DLCO	X							X	See Section 8.2.6. All patients: Required at D1 PLUS at any visit where there are new or significantly worsening clinical symptoms (pulmonary). Patients with an abnormal finding when compared to D1: all the above PLUS W26.
CCI									
CCI									
Clinical Safety Laboratory Assessments									
Urine pregnancy test	X	X		X	X	X		X	WOCBP only. Local laboratory test. Must be a highly sensitive urine pregnancy test.
CCI									

	OLE Treatment Period						Safety Follow-up ^c		Notes
Assessments and Procedures (Weeks)	0	4	8	12	24/ EOT	ET ^b	25	26	^a If within the window of the DBPC W24/EOT visit (W24+3 days; preferred option), participants should only complete the DBPC W24/EOT or OLE D1. If beyond this window, participants must attend both visits (DBPC W24/EOT and OLE D1). More than 2 weeks window between both visits requires prior approval from the Medical Monitor. ^b ET Study Visit should occur as soon as possible after premature discontinuation and replaces the EOT Visit. ^c Safety FU visits by phone and at site at 7 and 14 days, respectively, after ET or W24/EOT visit.
Study Day	1 ^a	29	57	85	169		176	183	
Visit Window (Days)		± 5	± 5	± 5	± 5	+ 5	+ 3	+ 3	
Routine urinalysis	X				X	X			See Appendix 5 . Samples can be collected pre or postdose.
Routine hematology, biochemistry	X	X		X	X	X		X	See Appendix 5 . Samples collected predose.
Muscle-associated enzymes	X	X		X	X	X		X	See Appendix 5 . Samples collected predose (as part of routine biochemistry).
Pharmacokinetic and CCI Assessments									
PK	X			X	X				Blood collected any time of the visit. See Section 8.4 .
CCI									CCI
CCI									CCI
CCI									CCI

Ab=antibody, CDASI=Cutaneous Dermatomyositis Area and Severity Index, C-SSRS=Columbia-Suicide Severity Rating Scale, CXR=chest X-ray D=Day, DBPC=Double-Blind Placebo Controlled, DLCO=Diffusing capacity of the lungs for carbon monoxide, DM=dermatomyositis, ECG=electrocardiogram, EOT=End of Treatment, ET=Early Termination, **CCI**, FU=follow-up, h=hour, HAQ-DI=Health Assessment Questionnaire-Disability Index, HBV=Hepatitis B virus, HRCT=high-resolution computed tomography, IgA=immunoglobulin A, IGA=Investigator's Global Assessment, IgG= immunoglobulin G, IgM=immunoglobulin M, **CCI**, MDAAT=Myositis Disease Activity Assessment Tool, MMT>manual muscle testing, OLE=Open Label Extension, PCR=polymerase chain reaction, PK=pharmacokinetic, PM=polymyositis, PtGA=Patient Global Activity, **CCI**, W=Week, WOCBP=women of childbearing potential.

Enpatoran is a small molecule, dual TLR7 and TLR8 antagonist **CCI**

The IIMs are a heterogeneous group of rare connective tissue diseases with clinical manifestations including muscle weakness due to inflammatory lesions in skeletal muscles. The pathogenesis of IIM is varied and not well understood, but evidence suggests that both the innate and adaptive arms of the immune system are involved (Dalakas 2015). T cells, autoantibodies produced by B cells, and Type I IFN have been implicated to play a role in driving disease pathogenesis. This study will focus on the DM and PM subsets of IIM. While PM disease manifestations are primarily restricted to muscle, DM pathology is observed in both muscle and skin.

CCI

TLR7 and TLR8 are transmembrane receptors that recognize single-stranded RNA. Activation of these receptors results in immune cell activation and inflammatory cytokine production (normally a protective host response) CCI

CCI

CCI

In addition to TLR7/8 activation by immune complexes, emerging evidence suggests that endogenous miRNA or viral RNA may trigger TLR7/8 activation and promote disease (Ye 2019; Kinder 2020; Mehta 2021).

Enpatoran is a potent, highly selective, small molecule dual TLR7/TLR8 antagonist shown to specifically inhibit TLR7/8 activation by various ligands such as single-stranded GU-rich RNAs (Vlach 2021). CCI

2.3 Benefit/Risk Assessment

There are limited guidelines that inform the management of IIM, but the standard of care is relatively uniform. First-line therapy usually includes glucocorticoids alone (starting dose of ~1 mg/kg daily, average dose of 60 mg prednisone equivalent; not normally exceeding 80 mg daily) or in combination with other immunosuppressants such as methotrexate or azathioprine. Second-line therapy includes glucocorticoids and mycophenolate mofetil, tacrolimus, or ciclosporin, or combination therapies such as azathioprine and methotrexate. Third-line therapy includes corticosteroids and rituximab, cyclophosphamide, repository corticotropin injection, or

other experimental biologic agents. Intravenous immunoglobulin (Octagam 10%) was recently approved in the US, UK and several European countries for treatment of DM, and has been used as a first-, second-, or third-line therapy alone or in combination with other immunosuppressants based on individual patient need. CS tapering can vary, but a reasonable approach is to drop the dose by 20% to 25% of the existing dose monthly with the goal of achieving a low (5 mg to 10 mg) daily dose of prednisone within 6 months (Oddis 2018). New therapeutic agents for IIM need to reduce the dependence on CS and toxic immunosuppressive agents, while also controlling end-organ damage, reducing morbidity, and mortality and improving the quality of life.

IIMs are heterogeneous disorders affecting the skeletal muscles, and PM and DM are the 2 major IIM subsets. Since IIM is relatively uncommon, randomized placebo-controlled trials are rare; consequently, optimal therapies are not adequately defined. The treatment objective is to improve muscle strength and avoid extra muscular complications. In patients with DM, resolution of cutaneous disease manifestations is an additional goal. As noted above and despite the absence of placebo-controlled trials demonstrating their effectiveness, glucocorticoids are the cornerstone of initial therapy for PM and DM. The significant drawbacks of long-term corticosteroid treatment are its side effects and, in some patients, insufficient efficacy. Side-effects of corticosteroid affected 32% to 41% of treated PM/DM patients (Baron 1985; Tymms 1985). Furthermore, disability was associated with corticosteroid therapy in long-term studies, especially osteonecrosis and osteoporotic vertebral fractures (Clarke 1995).

The current first-line glucocorticoid-sparing agent is usually either azathioprine or methotrexate (Oddis 2018). These drugs have not been compared directly in a clinical trial. Due to methotrexate induced hepatic and pulmonary toxicity, azathioprine is preferred in patients with interstitial lung disease related to myositis or who have underlying liver disease. Azathioprine is known to cause systemic flu-like reactions associated with fever, further gastrointestinal complaints develop in up to 12% of patients treated and lead to treatment discontinuation (Kissel 1986). Other side effects include bone marrow suppression, pancreatitis, and liver toxicity. Long-term side effects may include an increased risk of malignancy. Other treatment options include biologics, including rituximab and abatacept, which seem promising in some IIM patients. The available product data show that infections, neuropsychiatric toxicity (seizures, tremors, headache, dizziness, anxiety, nervousness, suicidal behavior and ideation, and psychotic disorder), cardiac disorder including ventricular arrhythmias and prolonged QT interval, hepatobiliary disorder, gastrointestinal (pancreatitis necrotizing) and immune system disorders have been experienced at variable frequency (very common to rare) by some patients on these therapies. Moreover, some of these drugs are associated with embryofetal development toxicity. CCI

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The clinical experience with enpatoran is limited to 3 completed studies in healthy participants (MS200569_0001, MS200569_0005, and MS200569_0040), 1 completed Phase 2 study in participants with COVID-19 pneumonia (MS200569_0026), 3 ongoing studies in SLE or CLE (MS200569_0004, MS200569_0003, and the LTE study MS200569_0048, which is enrolling

participants completing 24 weeks treatment in MS200569_0003). There is no similar class product available on the market. The following potential risks are being investigated based on the mechanism of action of a TLR7/8 antagonist and the nonclinical safety data of enpatoran (Table 3). The AEs consistent with conditions ascribed as potential risks will be closely monitored and reported as AESIs during the clinical development, e.g. CCI [REDACTED]

[REDACTED] All study participants will be made aware of signs and symptoms pertaining to contemplated potential risks and advised to report any adverse experiences throughout the study. CCI [REDACTED]

[REDACTED]

[REDACTED]

From the available data to date, enpatoran is well-tolerated demonstrating no significant toxicity in healthy participants nor in COVID-19 pneumonia patients. CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of enpatoran may be found in Section 2.3.1 and the IB.

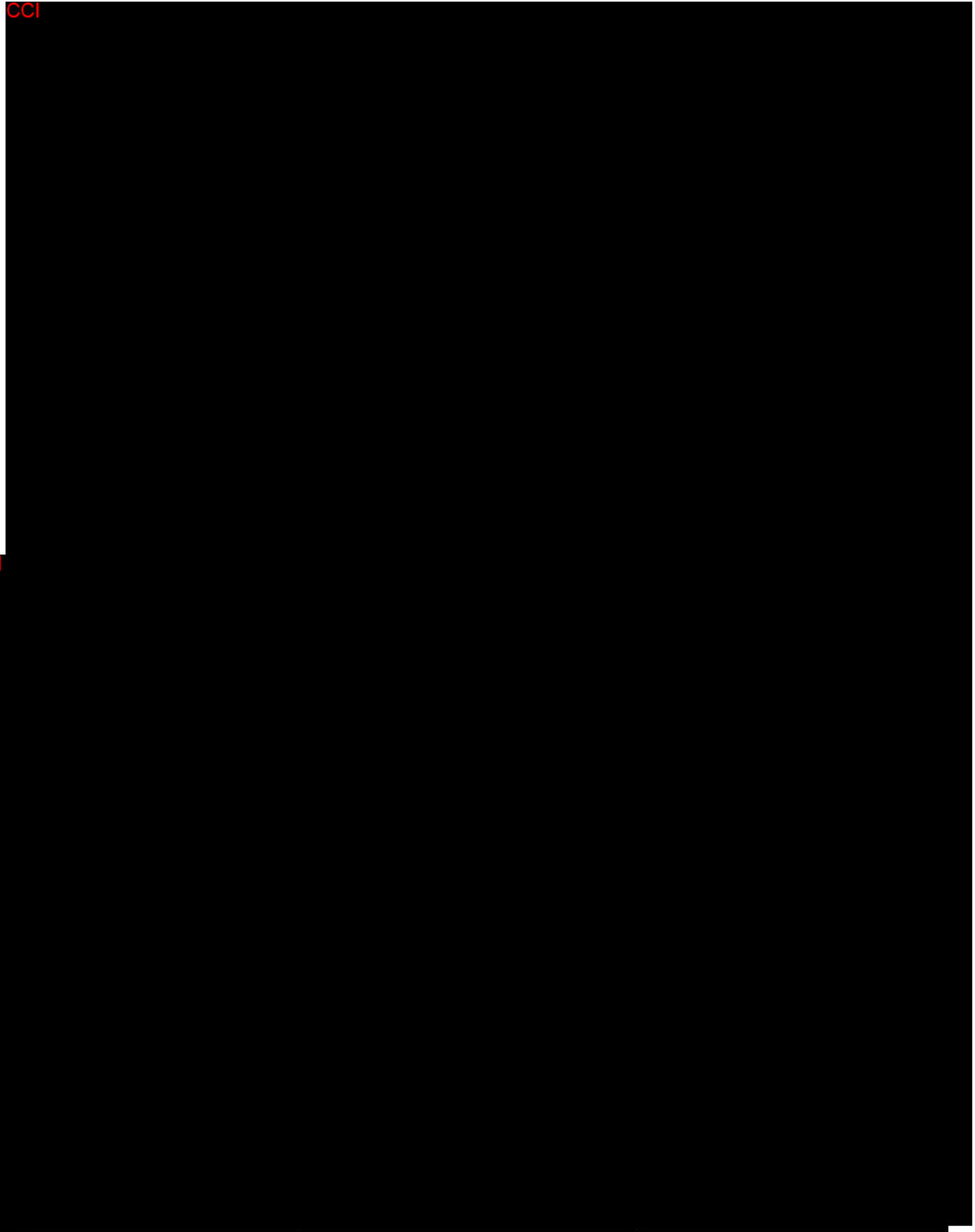
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[REDACTED]

2.3.1 Risk Assessment

CCI [REDACTED]

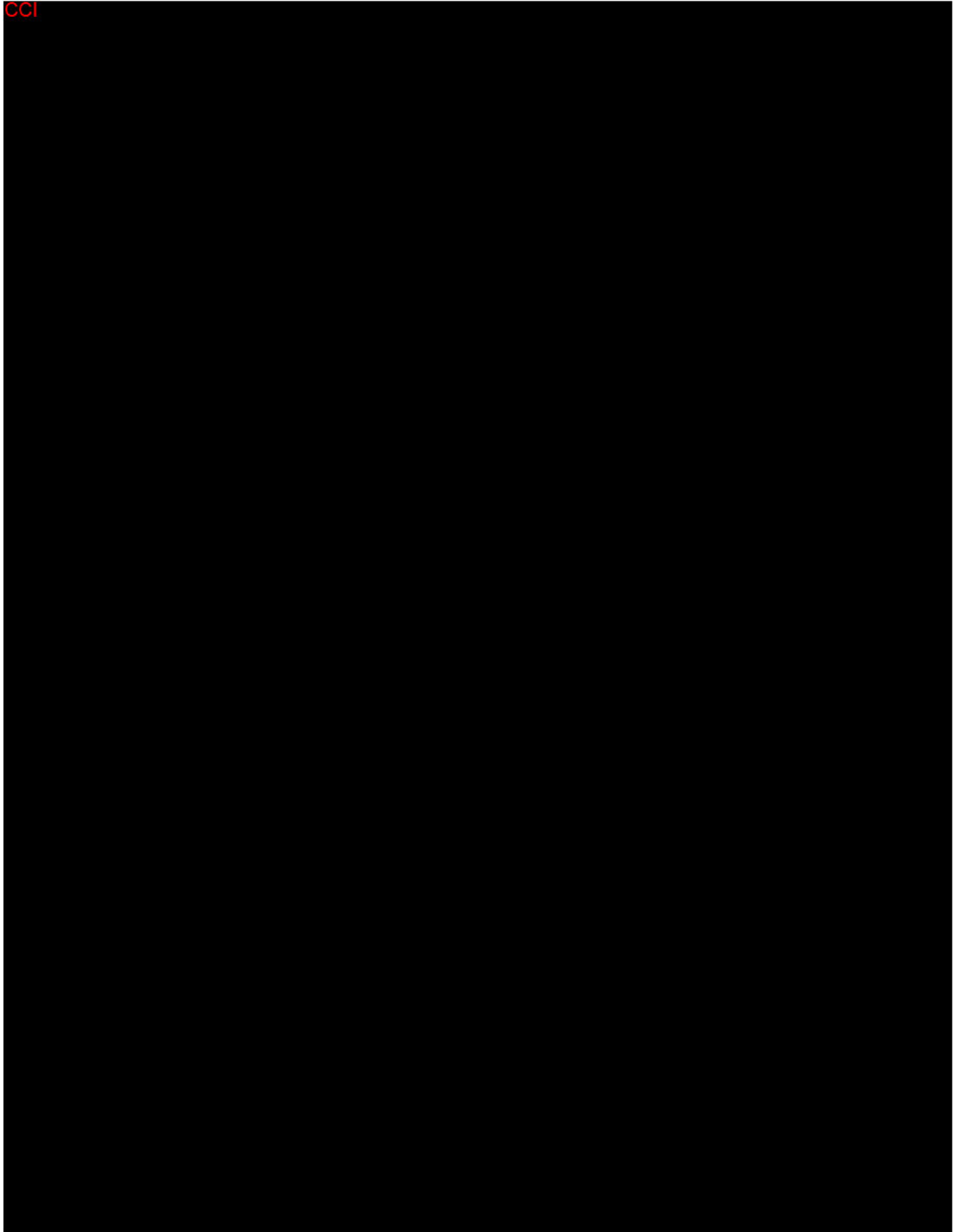
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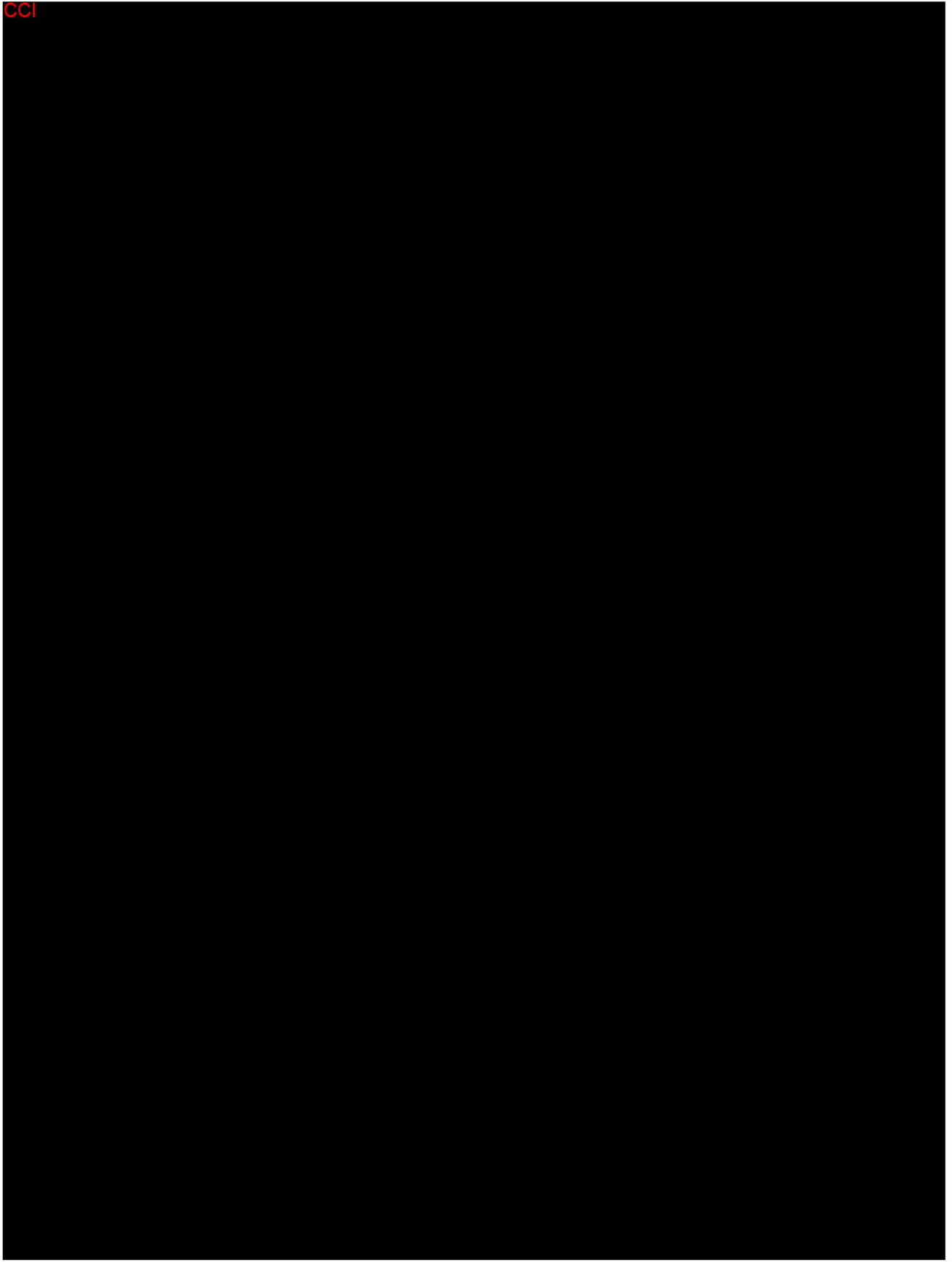
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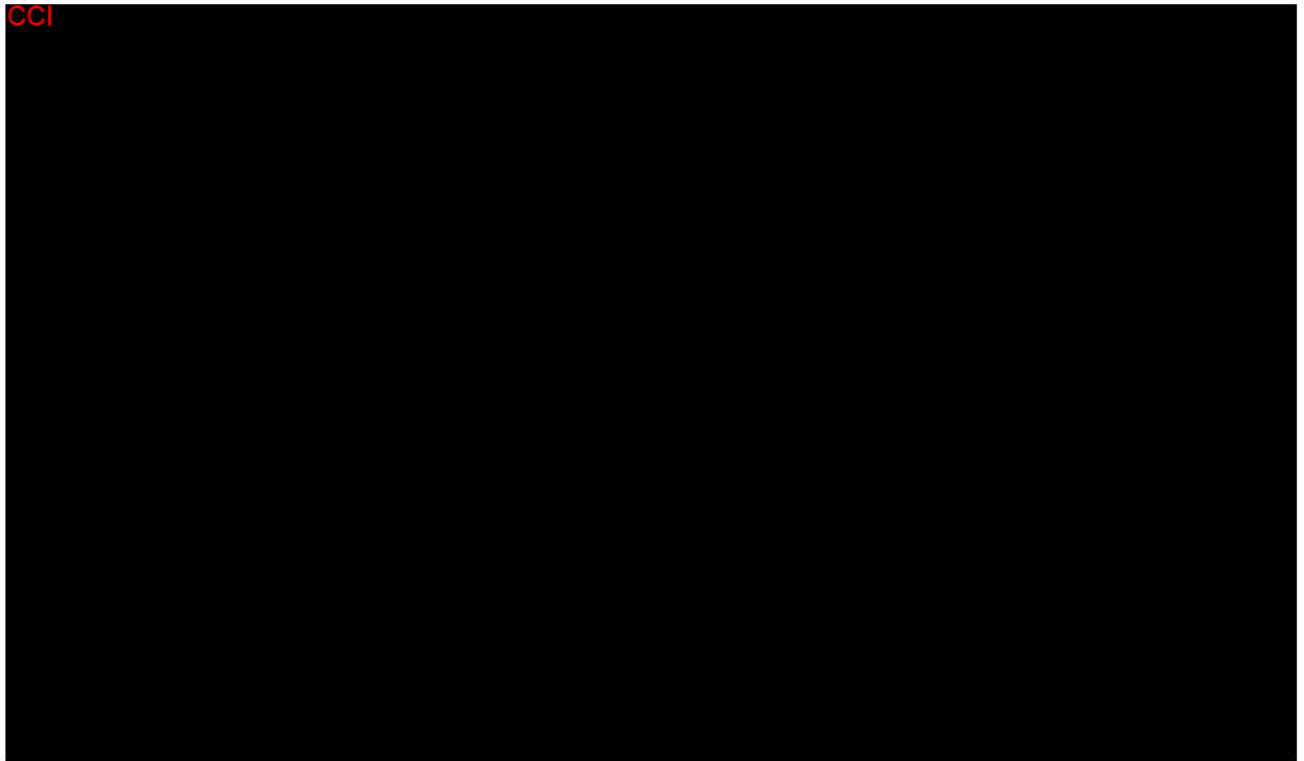


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2.3.2 Risk Assessment in the Context of SARS-CoV-2

Frequent and ongoing detailed risk assessments of the impact of the COVID-19 pandemic on the study will be performed. A risk mitigation plan will be in place if required, which takes into account current knowledge and also potential uncertainties. Details of the plan for maintaining study activities, including site initiation, monitoring, and close-out activities, will be included in the study Clinical Monitoring Plan.

2.3.3 COVID-19 Vaccination

The study participants are required to be up to date according to local guidelines on their vaccination with authorized COVID-19 vaccines. Should a potential study participant receive a COVID-19 vaccine prior to the study or during Screening Visit, the vaccination should not occur within 2 weeks before Day 1 study visit. Vaccination with an unauthorized COVID-19 vaccine is not permitted during the study.

2.3.4 Benefit Assessment

Enpatoran is currently being evaluated in multiple indications including CLE and SLE studies; albeit clinical benefit in the study participants is not confirmed. All study participants will be closely monitored and evaluated at regular intervals for enpatoran induced clinical response. This study will significantly contribute to further understanding of the immunopathogenesis of DM and PM.

CCI



2.3.5 Overall Benefit: Risk Conclusion

The anticipated benefits to patients with DM and PM are expected to outweigh the potential risks identified in association with enpatoran. Measures are taken to minimize the potential risks.

3 Objectives and Estimands

Objectives	Estimands	Ref. #
Primary		
To evaluate the effect of enpatoran compared to placebo on the ACR/EULAR TIS at Week 24 of the DBPC period in DM and PM participants	Endpoint: ACR/EULAR mean TIS (Aggarwal 2017) at Week 24, a weighted composite endpoint (range 0 to 100) derived from the absolute % improvement from baseline in the IMACS CSM: • PGA VAS derived from MDAAT • PtGA VAS • MMT-8 • HAQ-DI • Most abnormal muscle-associated enzymes • Extramuscular Activity Assessment derived from MDAAT	1
	Population: DM and PM patients Treatment: Enpatoran compared to placebo CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] Population-Level Summary: difference of means and 95% confidence intervals	
To evaluate the safety and tolerability of enpatoran in DM and PM participants during the DBPC period	Endpoints: • Occurrence of TEAEs, SAEs and AESIs during the DBPC period • Changes in laboratory parameters • Change in vital signs • Change in 12-lead ECG	2
	Population: DM and PM patients Treatment: Enpatoran compared to placebo Intercurrent Event Strategy: treatment policy Population-Level Summary: Descriptive statistics	

Objectives	Estimands	Ref. #
Secondary		
To evaluate the efficacy in disease control with enpatoran compared to placebo in DM and PM participants during the DBPC period	Endpoints: TIS Responder: • Occurrence of TIS ≥ 20 at Week 16, TIS ≥ 20 at Week 24 • Occurrence of TIS ≥ 40 at Week 16, TIS ≥ 40 at Week 24 • Occurrence of TIS ≥ 60 at Week 16, TIS ≥ 60 at Week 24 Population: DM and PM patients Treatment: Enpatoran compared to placebo CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] Population-Level Summary: number and % of participants with TIS ≥ 20, ≥ 40 or ≥ 60; differences to placebo with 95% CI; a participant is defined as responder if having a TIS score of ≥ 20 points and not having met any of the intercurrent events as defined in Appendix 8.	3
	Endpoints: • TIS at each visit from Week 4 up to and including Week 24 • PGA as derived from MDAAT at each visit from Week 4, up to and including Week 24 • PtGA at each visit from Week 4, up to and including Week 24 • Extramuscular Activity Assessment derived from MDAAT at each visit from Week 4, up to and including Week 24 • MMT-8 at each visit from Week 4, up to and including Week 24 • HAQ-DI at each visit from Week 4, up to and including Week 24 • Percent change from baseline in most abnormal muscle enzyme at each visit from Week 4, up to and including Week 24 • Absolute and % change for all above components	4

Objectives	Estimands	Ref. #
	Population: DM and PM patients Treatment: Enpatoran compared to placebo CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] Population-Level Summary: Difference of means and 95% CI	
	Endpoint: IMACS Responder, defined by the IMACS group DOI (Rider 2004), at Week 16 and at Week 24 as defined by: 3 of any 6 IMACS CSMs improved by $\geq 20\%$, with no more than 2 IMACS CSMs worse by $\geq 25\%$ (which cannot be MMT-8) Population: DM and PM patients Treatment: Enpatoran compared to placebo CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] Population Level Summary: Number and % of responders; difference from placebo with 95% CI	5

CONFIDENTIAL INFORMATION 41/132
CCI [REDACTED]

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DM and PM patients defined as per ACR/EULAR classification criteria, ASyS patients being defined as PM.
See [Appendix 8](#) for further details on CDASI-A, CDASI-D, IMACS CSM. Refer to [Rider 2017](#) and [Aggarwal 2017](#) for details on ACR/EULARI TIS.

CCI



ACR/EULAR=American College of Rheumatology/European League Against Rheumatism, AE=adverse event, AESI=adverse events of special interest, ASyS=anti-synthetase syndrome, CDASI=Cutaneous Dermatomyositis Area and Severity Index, CI=confidence interval, cm=centimeter, CS=corticosteroid, CSM=Core Set Measures, CCI, DBPC=Double-Blind Placebo Controlled, DM=dermatomyositis, DOI=definition of improvement, ECG=electrocardiogram, HAQ-DI=Health Assessment Questionnaire-Disability Index, HRQoL=health-related quality of life, CCI, IGA=Investigator's Global Assessment, CCI, IMACS=International Myositis Assessment and Clinical Studies, MDAAT=Myositis Disease Activity Assessment Tool, MMT>manual muscle testing, OLE=Open Label Extension, PGA=Physician Global Activity, PK=pharmacokinetic, PM=polymyositis, PtGA=Patient Global Activity, SAEs=serious adverse events, sec=second, CCI, TEAEs=treatment-emergent adverse events, TIS=Total Improvement Score, VAS=Visual Analog Scale.

a Disease worsening ([Oddis 2013](#)) is defined as meeting at least one of the following on 2 consecutive visits:

- Worsening of PGA by ≥ 2 cm on a 10 cm VAS and worsening on MMT-8 by $\geq 20\%$;
- Extramuscular Activity Assessment derived from MDAAT worsening by ≥ 2 cm on a 10 cm VAS;
- $\geq 30\%$ worsening in any 3 of the 5 IMACS CSMs (excluding the CSM "muscle-associated enzymes"; see [Appendix 8](#)).

4 Study Design

4.1 Overall Design

Study Design	Double-blind, parallel (see Study Schema in Section 1.2).
Control Method	Placebo-controlled
Single or Multicenter	Multicenter
Control Group	Placebo
Study Population Type	Patients with active DM or PM with moderate to severe myopathy treated with standard of care
Level and Method of Blinding	Double-blind, placebo
Bias Minimalization Method(s)	Blinding (see Section 6.3).
Study Intervention Assignment Method	Participants will be randomized 1:1 to enpatoran or placebo in permuted block with a stratification on the disease diagnosis at Screening (DM or PM as per 2017 ACR/EULAR classification criteria).
Involvement of Special Committee(s):	Yes (see Appendix 2)
Total Duration of Study Participation per Participant	Up to 31 weeks: (up to) 5-week Screening period, 24-week DBPC treatment period followed by a 2-week Safety Follow-up period. This Safety Follow-up period is not required for participants who enroll in the OLE period at Week 24. Optional OLE period: 26 weeks (24-week treatment period followed by a 2-week Safety Follow-up period).

Provisions for Study Extension or Entry into Roll-Over Studies	This study offers an optional OLE period for completers of the 24-week DBPC treatment period. For countries in which Authorities (local IRB/IEC or local Health Authorities) require submission of additional supporting information prior to start of OLE period, participation in the OLE period will only be offered after approval is received from the above Authorities.
Adaptive Aspects of Study Design	NA

ACR/EULAR=American College of Rheumatology/European League Against Rheumatism, DBPC=Double-Blind Placebo Controlled, DM=dermatomyositis, NA=not applicable, OLE=Open Label Extension, PM=polymyositis.

4.2 Scientific Rationale for Study Design

This is a proof-of-principle study designed to evaluate the safety and efficacy of enpatoran tablets taken orally twice a day for at least 24 weeks.

Participants will be randomized 1:1 to receive enpatoran 100 mg twice daily or placebo and stratified by disease diagnosis at Screening: PM vs DM stratification as per 2017 ACR/EULAR classification criteria. Stratification by disease diagnosis will facilitate efficient comparison of enpatoran to placebo within DM and PM. Balanced inclusion of DM and PM patients will be managed by IRT, targeting between 40% to 60% of patients with DM or PM.

CCI

There are 2 primary endpoints in this study; to evaluate the safety and tolerability of enpatoran in DM and PM participants during the DBPC period and to evaluate the effect of enpatoran compared to placebo on the ACR/EULAR TIS at Week 24 of the DBPC period in DM and PM participants.

The ACR/EULAR TIS is a weighted composite response criterion that combines 6 CSM of myositis disease activity. These CSM have been developed and validated by IMACS for use in DM and PM clinical trials. A total improvement score is determined by summing scores for each CSM, based on improvement (absolute percent change from baseline) in and relative weight of each core set measure. The TIS scale ranges from 0 to 100 with thresholds for minimal (≥ 20), moderate (≥ 40) and major (≥ 60) improvement in the combined 6 CSM (Aggarwal 2017).

The optional OLE treatment Period will provide data on long-term exposure and allow all completers of the DBPC period with the option to receive active enpatoran treatment. Only completers of the 24-week DBPC treatment period are eligible for the OLE period in order not to encourage early termination in the DBPC period.

4.3 Justification for Dose

For this proof-of-principle Phase IIa study 100 mg enpatoran twice daily, administered orally in a tablet formulation without food restriction, is proposed to be compared to placebo when given in addition to SoC in IIMs, specifically DM and PM patients, over a treatment duration of at least 24 weeks.

The following nonclinical and clinical data were considered when determining the 100 mg twice daily dose of enpatoran for this study:

CCI [REDACTED]

CCI [REDACTED]

[REDACTED]

[REDACTED]

Based on the above considerations, the proposed 100 mg twice daily dose in this Phase IIa study should provide the opportunity to evaluate a treatment effect of enpatoran compared to SoC in DM and PM patients with acceptable safety margins. The enpatoran dose during the OLE period may be modified based on emerging clinical safety data, without exceeding the highest clinically investigated and safe enpatoran dose.

For more details, refer to the IB.

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study. The data cut-off for primary analysis will be when the last participant completes the Week 24/End of Treatment visit of the DBPC period. The study will continue until completion of the OLE period.

A participant has completed the study if he/she has completed all study parts, including the Safety Follow-up visit. For participants of the optional OLE period, this would be once the OLE period (including the Safety Follow-up visit) has been completed.

5 Study Population

The criteria in Sections 5.1 and 5.2 are designed to enroll only participants, who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions are considered when deciding whether a participant is suitable for this study.

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

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative (where allowed by local laws and regulations) has provided written informed consent, as indicated in [Appendix 2](#).

The Investigator/sites will evaluate eligibility during Screening Visits (see [Table 1](#) for a list of assessments performed) and submit an eligibility packet (consisting of an eligibility checklist and appropriate documentation) for consented and potentially eligible participants. Based on this package, the eligibility team (Sponsor or designee, including Medical Monitor) will re-evaluate and confirm the eligibility. An IIM expert committee may be consulted by the eligibility team in case of doubts (but never on the expert's own patients). Clinical presentation of active myositis can also be confirmed by IIM expert committee based on a well-defined adjudication form. Participants will be randomized into the study after eligibility is confirmed by Investigator against the inclusion/exclusion criteria as listed in [Table 1](#) for Day 1.

Rescreening can occur as described in Section 5.4.

5.1 Inclusion Criteria

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

Category	Criterion
Age	1. Are ≥ 18 to ≤ 75 years of age at the time of signing the informed consent.
Type of Participant and Disease Characteristics	2. Are primarily diagnosed with DM or PM, meeting both criteria as described below: • Diagnosis of probable or definite DM or PM as per 2017 ACR/EULAR classification criteria (Lundberg 2017), probable IIM being defined as having a total score ≥ 5.5 or total score of ≥ 6.7 if biopsy data is available, definite IIM being defined as

Category	Criterion
	a total score ≥ 7.5 without muscle biopsy or ≥ 8.7 with muscle biopsy, and DM or PM subtype determined as per the subclassification criteria. - Positive autoantibody status (see Appendix 9). Historical data are acceptable. Note: ASyS patients that meet classification criteria are allowed, however, IMNM and IBM patients are excluded (see Exclusion Criteria 1). ASyS is defined as evidence of positive anti aminoacyl-tRNA synthetases autoantibodies (e.g. anti-Jo1, anti-EJ, anti-OJ, anti-PL7, anti-PL12, anti-KS, anti-HA, anti-YRS, anti-Zo). 3. Active disease on SoC, must meet 1 of the below criteria (Note: The Investigator can request eligibility determination by an IIM expert committee based on clinical presentation of active myositis for those patients with suspected active disease not meeting any of the below criteria) - Pathological evidence of active myositis in muscle biopsy within 6 months prior to Screening (to be met before Screening) - Evidence of active myositis by electromyography within the last 6 months prior to Screening (to be met before Screening) - MRI with evidence of active myositis within the last 6 months prior to Screening (to be met before Screening) - Any muscle enzyme $\geq 4 \times$ ULN at time of Screening - Active PM/DM skin rash as per CDASI-A ≥ 7 at time of Screening 4. Disease severity as defined by moderate to severe myopathy with MMT-8 ≥ 80 and ≤ 142 AND at least 2 of the following CSM abnormalities: - PtGA ≥ 2 cm - PGA derived from MDAAT ≥ 2 cm - Extramuscular Activity Assessment derived from MDAAT ≥ 2 cm - At least 1 muscle enzyme > 1.5 times ULN - HAQ-DI ≥ 0.25

Category	Criterion
Current Therapy	5. Stable doses of oral CS and/or maximum of 1 non-corticosteroid immunosuppressive/immunomodulatory medications (methotrexate, 6-mercaptopurine, sulfasalazine, mycophenolate mofetil or sodium, azathioprine, leflunomide, cyclosporine, oral tacrolimus) for DM or PM as defined by the following: a. Oral CS: Treatment must have initiated ≥ 12 weeks prior to Screening Visit. Unchanged dose of oral CS ≤ 20 mg per daily prednisone-equivalent for at least 4 weeks before Screening Visit. b. Immunosuppressive/immunomodulatory medications: Treatment must have initiated ≥ 16 weeks prior to Screening Visit. Unchanged dose of immunosuppressive medications other than oral CS for ≥ 8 weeks before Screening Visit. Note: In addition, antimalarials are allowed with stable doses ≥ 12 weeks before Screening Visit (hydroxychloroquine up to 400 mg/day).
Weight	6. Have a BMI lower or equal to 40.0 kg/m².
Sex and Contraception/Barrier Requirements	7. All sexes allowed. The Investigator confirms that each participant agrees to use appropriate contraception and barriers, if applicable. The contraception, barrier, and pregnancy testing requirements are below. Contraceptive use will be consistent with local regulations on contraception methods for those participating in clinical studies. a) Female participant: - Is not breastfeeding - Is not pregnant (i.e., has a negative serum pregnancy test, as required by local regulations, confirmed with a highly sensitive urine test within 24 hours before the first dose of study intervention). - Is not a WOCBP - If a WOCBP, use a highly effective contraceptive method (i.e., with a failure rate of $< 1\%$ per year), preferably with low user dependency, as described in Appendix 3 for the following time periods:

Category	Criterion
	1. Before the first dose of the study intervention, if using hormonal contraception: ○ Has completed at least one 4-Week cycle of an oral contraception pill and either had or has begun her menses. OR ○ Has used a depot contraceptive or extended-cycle oral contraceptive for least 28 days and has a documented negative pregnancy test using a highly sensitive assay. OR ○ Has used a barrier method, as described in Appendix 3. 2. During the intervention period. 3. After the study intervention period (i.e., after the last dose of study intervention is administered): for at least 90 days after the last dose of study intervention and agree not to donate eggs (ova, oocytes) for reproduction during this period. The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study intervention. The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy. b) Male participant: Agree to the following during the study intervention period and for at least 90 days (a spermatogenesis cycle) after the last dose of study intervention. • Refrain from donating fresh unwashed semen. PLUS, either: • Abstain from any activity that allows for exposure to ejaculate. OR • Use a male condom: • When having sexual intercourse with a WOCBP, who is not currently pregnant, and instruct her to use a highly effective contraceptive method with a failure rate of < 1% per year, as described in Appendix 3, since a condom may break or leak.

Category	Criterion
	• When engaging in any activity that allows for exposure to ejaculate.
Informed Consent	8. Capable of giving signed informed consent, as indicated in Appendix 2 , which includes compliance with the requirements and restrictions listed in the ICF and this protocol.
Vaccinations	9. Are up to date with vaccination, according to local guidelines for specific patient population (e.g., taking immunosuppressive, participating in clinical studies), against Streptococcus pneumoniae, influenza virus (as seasonally required for influenza virus) and SARS-CoV-2.

5.1.1 Inclusion Criteria for Entry into Open Label Extension

Participants are eligible to be included in the optional OLE Period only if all the following criteria apply:

1. Have completed the 24-week DBPC Treatment Period of the study. More than 2 weeks window between DBPC Week 24 and OLE Day 1 visits requires prior approval from the Medical Monitor. Medical Monitor will evaluate whether any protocol safety assessments require repeating prior to enpatoran treatment continuation.
2. Continue to agree to follow the contraception/barrier requirements specified in Section 5.1 and WOCBP have a negative highly sensitive urine pregnancy test.
3. Continue being up to date with vaccination, according to local guidelines, against Streptococcus pneumoniae, influenza virus (as seasonally required for influenza virus) and SARS-CoV-2.
4. Have signed written informed consent for OLE period. Capable of giving signed informed consent, as indicated in [Appendix 2](#), which includes compliance with the requirements and restrictions listed in the ICF and this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Category	Criterion
Medical Conditions	1. Primary diagnosis of IBM, malignancy-associated myositis (defined as diagnosis of myositis within 3 years of cancer), IMNM with a biopsy characterized as necrotizing biopsy or IMNM with positive anti-SRP or anti-HMGCR auto-antibodies. Patients with anti-TIF-1 gamma antibody or newly diagnosed (within 1 year) anti MDAT5 antibody should have had adequate screening for cancer within 12 months of Day 1. Adequate screening of cancer is defined as up-to-date age and gender appropriate screening as per national guidelines.
	2. Primary diagnosis of juvenile DM, or adult patients previously diagnosed with juvenile DM.
	3. Any other active concurrent connective tissue disease associated with inflammatory myopathy in the Investigator's opinion. Eligibility of participants with diagnosis of concurrent connective tissue disease(s) will be reviewed and approved by an IIM expert committee.
	4. Severe interstitial lung disease defined as supplemental O₂ required at rest, or FVC of < 60% predicted. Patients within 1 year of PM/DM diagnosis and anti-MDA5 antibody, should have been evaluated for interstitial lung disease with high-resolution CT chest.
	5. Any uncontrolled disease (e.g. severe respiratory, cardiovascular, gastrointestinal, neurological, psychiatric, hematological, metabolic [including thyroiditis with increased/decreased TSH], renal [eGFR < 40 mL/min/1.73 m² as calculated by the Modification of Diet in Renal Disease equation by the central laboratory], hepatic, endocrine/reproductive organ disease) other than DM/PM, that in the Investigator's or Sponsor/designee's opinion constitutes an inappropriate risk or contraindication for participation in the study or that could interfere with the study objectives, conduct, or evaluation.

Category	Criterion
	6. History of epilepsy, other neurological or neuromuscular disorder with seizure propensity.
	7. Significant cardiovascular events (e.g., acute myocardial infarction, unstable angina or peripheral vascular disease symptoms, hospitalization for congestive heart failure, uncontrolled or New York Heart Association Class 3 or 4 congestive heart failure, cardiac surgery, ischemic or hemorrhagic stroke, or transient ischemic attack) $\leq$ 6 months before Screening Visit. Family history of sudden cardiac death, unexplained death, long QT syndrome, or death from a primary dysrhythmia potentially associated with QT prolongation in any family member.
	8. Active or unstable (not controlled by medical intervention) cardiac arrhythmia or clinically significant abnormality on ECG at Screening Visit or Day 1 that in the Investigator's or Sponsor/designee's opinion constitutes inappropriate risk or contraindication for study participation or could interfere with study objectives, conduct or evaluation. This includes but is not limited to clinical conditions, asymptomatic QTcF $\geq$ 450 ms in men or $\geq$ 470 ms in women at baseline which is persistent on reassessment, or unstable cardiovascular disease; history of undiagnosed, or sudden loss of consciousness, long QT syndrome, Wolff Parkinson White syndrome, or a malignant ventricular arrhythmia (e.g. ventricular fibrillation or ventricular tachycardia) unless treated. Note: any sinus bradycardia or tachycardia detected in the ECG and consistent with the medical history will not be exclusionary unless other ECG abnormalities are identified. Clinically abnormal electrolytes during Screening that cannot be corrected.

Category	Criterion
	9. Ongoing or active clinically significant viral (including SARS-CoV-2), bacterial or fungal infection, or any major episode of infection requiring hospitalization or completed treatment with parenteral anti-infectives ≤ 4 weeks prior to or during Screening Period, or completion of oral anti-infectives ≤ 2 weeks prior to Screening Visit. Vaginal candidiasis, onychomycosis, and genital or oral herpes simplex virus considered to be sufficiently controlled will not be exclusionary. Investigators should follow their local guidelines for SARS-CoV-2 testing during or before the Screening period (e.g., asymptomatic testing is required before entering a research study, symptomatic/exposure-based screening only). In addition, within 3 to 5 days prior to randomization, all participants should be specifically questioned for COVID-19 symptoms or close contact to a person with SARS-CoV-2 infection to determine if SARS-CoV-2 testing (accepted according to local guidelines) should be performed (or repeated).
	10. Any of the following: a. A positive HIV test. b. Positive HCV Ab and detectable HCV RNA performed reflexively at Screening, <u>or</u> history of treated HCV with detectable HCV RNA performed reflexively at Screening. c. Positive HBV surface antigen, <u>or</u> positive HBV core Ab with negative HBV surface Ab and reflexive detectable HBV DNA at Screening, <u>or</u> no history of HBV vaccination with positive HBV surface and/or core Abs and reflexive detectable HBV DNA at Screening.

11. Any of the following:

- a. History of active TB.

Note: patients with a history of active or latent TB who have documented evidence of appropriate treatment and with no history of re-exposure since their treatment was completed would not be required to undergo the protocol specific TB testing for PPD, QuantiFERON test or T-SPOT test, but would still require a baseline chest X-ray to rule out active TB and documentation of completed treatment”.

- b. Current diagnosis of active TB.

- c. Untreated LTBI.

- d. Undergoing current treatment for LTBI.

- e. Participants with current household contacts with active TB.

In the absence of an active TB diagnosis, or clinical features consistent with an active TB diagnosis, LTBI is determined by any of the following:

- Prior TB skin test with purified protein derivative with induration ≥ 5 mm (unless vaccinated with Bacille Calmette-Guérin).
- Prior positive T-SPOT.TB (Elispot) result.
- Positive QuantiFERON test, either at Screening or with documented past results.

Note: All participants, except those who have previously completed appropriate and documented LTBI treatment, must undergo QuantiFERON testing during Screening. Participants with indeterminate or positive QuantiFERON results that may represent a false positive as assessed by the Investigator, with no clinical features consistent with active TB, will be evaluated with either a repeat QuantiFERON test or a T-SPOT.TB test at the request of the Investigator (allowed locally). In the case of a negative QuantiFERON or T-SPOT.TB result, the participant may be enrolled after approval by the study eligibility team. If the repeat QuantiFERON result is indeterminate, the participant will be excluded.

Category	Criterion
	12. Significant suicide risk in the last year (including suicidal ideation and/or suicidal behavior on the C-SSRS during Screening).
	13. History of or planned solid organ transplant.
	14. History of splenectomy or functional asplenia.
	15. Any major surgery such as abdominal, thoracic, or joint replacement surgeries ≤ 6 weeks prior to Screening Visit or planned major surgery during the study (including Follow-up).
	16. History of alcohol or drug abuse ≤ 1 year prior to Screening Visit.
	17. History of malignancy (hematologic or solid tumor) within 5 years prior to Screening Visit, except adequately treated basal cell or squamous cell carcinomas of the skin (≤ 3 lesions requiring treatment in lifetime) or adequately treated carcinoma in situ/cervical intraepithelial neoplasia of the uterine cervix.

Prior/Concomitant Therapy	18. Known hypersensitivity to any study intervention, component, or placebo. 19. The use, initiation, or dose change in the following therapies: a. Use of topical corticosteroids ≤ 2 weeks prior to Screening. b. Use of intramuscular or injectable CS ≤ 4 weeks prior to Screening (intralesional therapies to be stopped 2 weeks prior to Screening). c. Use of CS exceeding 20 mg daily prednisone-equivalent for DM and PM (any dosage form) ≤ 4 weeks prior to Screening (Table 5). d. Use of topical calcineurin inhibitors (e.g., pimecrolimus) ≤ 2 weeks prior to Screening. Oral tacrolimus up to 0.1 mg/kg is permitted. e. Initiation or dose change of NSAIDs above maximum prescribed dose per local label ≤ 2 weeks prior to Screening. f. Vaccination with a subunit or inactivated vaccine (vaccination during study is allowed) ≤ 2 weeks prior to Day 1. 20. Vaccination with live or live attenuated virus vaccine ≤ 4 weeks prior to Day 1. 21. The use of the following therapies: a. ≤ 12 weeks prior to Day 1: intravenous or subcutaneous Ig (exception: ≤ 8 weeks prior to Day 1 if only ≤ 2 doses Ig received), abatacept, antitumor necrosis factor alpha agents, plasmapheresis, cyclophosphamide, or other disease modifying, immunosuppressive or immunomodulatory therapies not otherwise specified in the protocol (see Sections 5.1 and 6.8.2). b. ≤ 24 weeks prior to Day 1 (unless a different time frame is indicated): B cell depleting/modulating therapy such as anti-CD20 agents (e.g., rituximab, telitacicept, atacicept), dual or other anti-B Lymphocyte stimulator/proliferation inducing ligand neutralizing
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	therapies (exception belimumab: ≤ 16 weeks prior to Day 1) (see Appendix 6). c. ≤ 24 weeks prior to Day 1: IL-12/IL-23 pathway inhibitors (e.g., ustekinumab). d. ≤ 24 weeks prior to Day 1: Anti-IL-6 receptor (tocilizumab, sarilumab) or anti-IL-6 (siltuximab). e. ≤ 24 weeks prior to Day 1: Anti-IL-1 receptors or anti-IL-1 agents. f. ≤ 24 weeks prior to Day 1: Type 1 IFN pathways inhibitors (e.g., anifrolumab). g. ≤ 4 weeks prior Day 1: JAK-STAT pathway inhibitors (tofacitinib). h. ≤ 12 weeks (or 5 half-lives, whichever is longer) prior Day 1: treatments approved only for non-IIM indications (e.g. ravulizumab, efgartigimod). Treatment of lung fibrosis with nintedanib and pirfenidone is permitted.
22.	CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED]
23.	Use of following medications associated with CCI [REDACTED] within 2 weeks or 5 half-lives, whichever is longer, prior to Day 1: a. Antidepressants: CCI [REDACTED] [REDACTED] tricyclic antidepressants, monoamine oxidase inhibitors, lithium. b. Analgesics: tramadol, pethidine, fentanyl, dextromethorphan (e.g., in OTC cough remedies). c. CCI [REDACTED] [REDACTED] [REDACTED] d. Antibiotics: Linezolid, tedizolid. e. Tryptophan. f. Anxiolytic: Buspirone.

Category	Criterion
	g. Methylthioninium chloride (methylene 75 blue). Note: For patients on any of these drugs for > 3 months or requiring continuation, use might be permitted if switching to lowest effective dose is considered by the Investigator (in consultation with the prescribing specialist) and discussed with the participant and the Medical Monitor (only allowed for 1 drug). 24. Initiation or planning to start an exercise program for muscle strengthening within 4 weeks of Day 1 or planned initiation of a muscle strengthening exercise program during the study up to Week 24. Physical therapy-directed exercise regimen is allowed if started ≥ 4 weeks prior to Day 1 and kept on stable schedule, frequency and extend up to Week 24. Any such exercise regimen must be documented.
Prior/Concurrent Clinical Study Experience	25. Treatment with other investigational agents within the last 12 weeks or 5 half-lives or as per washout requirement from the previous protocol, whichever is longest, prior to Day 1.
Diagnostic Assessments	26. Clinically significant or predefined abnormalities in laboratory tests at Screening Visit unless the liver test elevation is consistent with muscle origin: a. AST or ALT $> 3 \times \text{ULN}$ and total bilirubin $> 2 \times \text{ULN}$ b. AST or ALT $> 2.5 \times \text{ULN}$ and total bilirubin $> 2 \times \text{ULN}$ and INR elevation Isolated elevation of AST or ALT $> 2.5 \times \text{ULN}$ without any other liver or muscle enzyme elevation should be discussed with medical monitor. Hemoglobin $< 5.0 \text{ mmol/L}$ (9 g/dL), white blood cells $< 2.5 \times 10^9/\text{L}$, absolute neutrophil count $< 1,500/\text{mm}^3$, or platelets $< 75 \times 10^9/\text{L}$.

Category	Criterion
	27. Signs of significant abnormalities on chest imaging e.g., new (not previously documented) interstitial lung disease or with significant changes from previous assessment. Chest imaging as per chest X-ray, computer tomography, MRI; acceptable if done within 6 months before Screening if no clinical changes are suspected.
Other Exclusions	28. Significant improvement between Screening and Day 1 defined as meeting at least one of the following: Meeting one of the following: • More than 2 points change at Day 1 compared to Screening in PGA VAS. • More than 5 points change at Day 1 compared to Screening in MMT-8. OR meeting two of the following: • More than 2 points change at Day 1 compared to Screening PtGA VAS. • More than 2 points change at Day 1 compared to Screening Extramuscular Activity Assessment VAS. • More than 0.6 points change at Day 1 compared to Screening in HAQ-DI. • More than 6 points change at Day 1 compared to Screening in CDASI.

5.2.1 Exclusion Criteria for Open Label Extension Period

Participants are excluded from the OLE Period if any of the following criteria apply:

1. Participants who experienced serious event(s) related to the study intervention during the DBPC period, an unstable medical condition, or any other reason, in the opinion of the Investigator or Sponsor/designee that would preclude participation in the OLE Period.
2. Other severe acute or chronic medical or psychiatric condition that in the Investigator's or Sponsor/designee's opinion constitutes an inappropriate risk or contraindication for participation in the study or that could interfere with the study objectives, conduct, or evaluation.
3. Received any OLE prohibited medication after the DBPC Week 24/End of Treatment Visit.
4. Planned major elective medical or surgical procedure during the study or major surgery performed ≤ 6 weeks before OLE Day 1.

5. Breastfeeding/lactating women. Lactating women are excluded regardless of whether or not they are nursing infant(s).
6. Participation in any investigational agent study after the DBPC Week 24/End of Treatment Visit.
7. For participants with more than 2 weeks window between DBPC Week 24/End of Treatment and OLE Day 1 (in case Medical Monitor approves participation): Reconfirm main study Exclusion Criteria [5](#), [7](#), [8](#), [9](#), [12](#), [16](#), [18](#), [20](#), [24](#), and [26](#) (see Section [5.2](#)).

5.3 Lifestyle Considerations

Participants are recommended to continue to use sunscreen.

5.3.1 Meals and Dietary Restrictions

No food restrictions. On scheduled study visit days with PK assessment (see Section [1.2](#)), record the date and time of the closest meal before and after the study intervention administration.

5.3.2 Activity

Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities (e.g., watching television or reading).

5.4 Screen Failures

Retesting

During the initial Screening Period or single rescreening period, testing may be repeated once for participants if test results would preclude enrollment in the study and are thought to represent a laboratory error, or a reversible, clinically insignificant intermittent condition, or are inconsistent with the patient's historical values.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants will be assigned a new participant number.

If a participant is rescreened, all Screening tests should be repeated with the exception of:

- Hepatitis and HIV testing must have occurred within 1 month of the initial Rescreening Visit or will need to be repeated during the Rescreening Period.
- Documented TB testing must have occurred within 3 months of the initial Rescreening Visit or need to be repeated during the Rescreening Period.
- Documented chest imaging must have occurred within 6 months of the Rescreening Period otherwise to be repeated during the Rescreening Period.

5.5 Criteria for Temporarily Delaying the Enrollment/Randomization/Administration of Study Intervention Administration

Not applicable.

6 Study Intervention(s) and Concomitant Therapies

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

6.1 Study Intervention(s) Administration

Participants will self-administer study intervention twice per day (every 12 hours $\pm$ 2 hours) (see Sections 1.3.1 and 1.3.2). CCI

On scheduled study visit days, the participant will be asked not to self-administer study intervention at home but to bring the study intervention to the site for administration after the scheduled study visit assessment/procedures are performed (other than post treatment ECGs and PK/PD sampling). Last dose of DBPC period study intervention to be administered the day before DBPC End of Treatment in order that only OLE study intervention is received on OLE Day 1. Study intervention will be administered up to but not including End of Treatment/Early Termination visit.

Arm Name	Enpatoran: DBPC period	Placebo: DBPC period	Enpatoran: OLE period
Arm Type	Experimental	Placebo Comparator	Experimental
Intervention Name	Enpatoran	Placebo	Enpatoran
Type	Drug	Drug	Drug
Dose Formulation	CCI [REDACTED]	[REDACTED]	[REDACTED]
[REDACTED] [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dose Amount	100 mg CCI [REDACTED] [REDACTED]	CCI [REDACTED]	100 mg CCI [REDACTED] [REDACTED]
Frequency	twice daily	twice daily	twice daily
Route of Administration	Oral	Oral	Oral
Use	Experimental	Placebo comparator	Experimental
IMP/NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor.	Provided centrally by the Sponsor.	Provided centrally by the Sponsor.
Packaging and Labeling	Study Intervention will be provided in wallets containing 24 units in CCI [REDACTED]. Each wallet will be labeled per country requirement and Good Manufacturing Practice Guidelines.	Study Intervention will be provided in wallets containing 24 units in CCI [REDACTED]. Each wallet will be labeled per country requirement and Good Manufacturing Practice Guidelines.	Study Intervention will be provided in wallets containing 24 units in CCI [REDACTED]. Each wallet will be labeled per country requirement and Good Manufacturing Practice Guidelines.
Current/Former Name(s) or Alias(es)	M5049	-	M5049

DBPC=Double-Blind Placebo Controlled, IMP=investigational medicinal product, M5049=enpatoran, NIMP=noninvestigational medicinal product, OLE=Open Label Extension.

6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability

CCI [REDACTED]
[REDACTED]

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Upon receipt of the study intervention(s), the Investigator or designee will confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery. Further guidance and information for study intervention accountability are provided in the Study Reference Manual.

- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) will be stored in a secure, environmentally controlled, and monitored (manual or automated) area, per the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
 - Confirmation of receipt, in good condition and in the defined temperature range.
 - The inventory provided for the clinical study and prepared at the site.
 - The dose(s) each participant used during the study.
 - The disposition (including return, if applicable) of any unused study intervention(s).
 - Dates, quantities, batch numbers, blister package numbers, expiry dates, and the participant numbers.
- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) will not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Study Reference Manual.
- Participants will record date, time, kit number and amount of study intervention administration and whether a meal was consumed within 1 hour predose or 2 hours postdose in the paper diary card or mobile application provided.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

After confirmation of participant's eligibility and at the last practical moment prior to study intervention administration, participants will be centrally allocated to either enpatoran 100 mg twice daily or placebo twice daily in a 1:1 ratio using an IRT and per a computer-generated randomization list.

Participants will be randomized in permuted block and stratified by disease diagnosis at Screening: DM or PM as per 2017 ACR/EULAR classification criteria. Balanced inclusion of DM and PM patients will be managed by IRT, targeting between 40% to 60% of patients with DM or PM.

The IRT will be used to assign unique participant numbers, allocate participants to study

intervention group at the Randomization Visit, and allocate study intervention to participants at each study intervention visit in DBPC period.

Before the study is initiated, the directions for the IRT will be provided to each site. The site will contact the IRT prior to starting study intervention administration for each participant.

During OLE, all participants will receive enpatoran 100 mg twice daily and the study intervention will be dispensed via IRT.

6.3.2 Blinding

Blinding Method

The study will be double-blind during the 24-week DBPC period. Enpatoran and placebo tablets are identical in size, color, and appearance.

Randomization codes will be kept strictly confidential, accessible only to authorized staff, until the time of unblinding. All other study related individuals, ancillary site staff, clinical research associates/monitors, the Investigator, Sponsor, and CRO staff will remain blinded to study intervention.

The drug codes will only be broken and made available for the data analysis once the last participant reaches 24 weeks of study intervention or discontinues study intervention prematurely, the protocol deviations are determined, and the database is locked for the primary analysis.

After primary analysis of the DBPC period, sites and participants will remain blinded to the DBPC assignment as feasible. During OLE, all participants will receive enpatoran in an open label fashion but will remain blinded to the treatment received during the DBPC period.

The IDMC will review unblinded study information during the conduct of the study (details will be provided in the IDMC charter). The Firewall team may review unblinded study information (details will be provided in the Firewall Team charter).

The analytical laboratories responsible for analyses of the PK samples (requiring shipment of laboratory samples from the site) will be unblinded to study treatment codes to enable sample testing of enpatoran PK prior to database lock. Masked participant identifiers will be used to support association of PK data with treatment codes while preventing association of treatment codes with any other clinical data, such as safety and clinical response data.

Laboratory analysis information that may unblind the study participants will not be reported with participant identifiers to investigative sites or blinded personnel until the study has been unblinded.

Assignment Method Retention

The study blind may be broken in the event emergency unblinding is necessary for participant safety or the reporting of SUSARs.

Unblinding in these cases would be done via the unblinding module in IRT. All breaks of the study blind must be adequately documented.

6.3.3 Emergency Unblinding

In an emergency, the Investigator is solely responsible for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety is always the first consideration in this decision. If the Investigator decides that unblinding is warranted, the Investigator makes every effort to contact the Sponsor prior to the unblinding, unless this could delay emergency treatment. The Sponsor will be notified within 24 hours after unblinding. The Investigator will provide the Sponsor the reason for unblinding without revealing the study intervention, except to the designated global patient safety representative via the Emergency Unblinding Notification Form. The date of and reason for unblinding will be recorded in the source documents and CRF. Contact information for unblinding in an emergency is given on the participant emergency card provided to each participant, as noted in [Appendix 2](#).

The Sponsor's global patient safety department will submit any SUSAR reports to regulatory authorities and ethics committees with unblinded information, per applicable regulations. Only blinded information will be provided to the study team.

Participants undergoing emergency unblinding will be discontinued from the study intervention. The investigations scheduled for the ET and Safety Follow-up Visit should be performed (see Section [7.1](#)).

6.4 Study Intervention Compliance

Besides study visits where study intervention will be administered under medical supervision at the site, study participants will self-administer their study intervention at home. They will be provided with a diary card or phone application containing instructions for self-administration and documentation of study intervention intake. If participants use the phone application, they may also receive reminders to administer study intervention and perform related documentation.

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, and review of diary cards or data generated from the phone application using the vendors portal during the site visits and documented in the source documents and CRF. Any deviation(s) from the prescribed dosage regimen are recorded in the CRF.

A record of the number of tablets dispensed to and taken by each participant will be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.5 Dose Modification

Dose modifications are not allowed.

6.6 Continued Access to Study Intervention after the End of the Study

The Sponsor will not provide any additional care to participants after they leave the study because such care would not differ from what is normally expected for patients with PM or DM.

6.7 Treatment of Overdose

For this study, any dose of enpatoran greater than 300 mg CCI within 24 hours $\pm$ 2 hours or a single dose greater than 200 mg CCI will be considered an overdose.

The Sponsor has no specific recommendation for treating an overdose. The Investigator will use his/her clinical judgment to manage any overdose, considering the symptoms and any site procedures or standards.

Even if not associated with an AE or a SAE, any overdose is recorded in the CRF and reported to global patient safety in an expedited manner. Overdoses are reported on a SAE and Overdose Report Form, following the procedure in [Appendix 4](#).

6.8 Concomitant Therapy

Record in the CRF all concomitant therapies (e.g., medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

6.8.1 Corticosteroids

6.8.1.1 Corticosteroid Tapering

CS tapering guidance and targets will be implemented in this study (see [Figure 2](#)). Long-term use of CSs should be minimized since its use has been associated with damage and morbidity ([Choy 2002](#)). Inhibitors of type I IFN pathway are potentially corticosteroid-sparing by increasing glucocorticoid sensitization ([Guiducci 2010](#)).

To demonstrate the potential CS-sparing effect of enpatoran and its treatment effect compared with placebo, it is critical that medical management of these participants must include tapering of CS use.

Starting at Week 8 (Study Day 57), Investigators **MUST** taper CS as clinically tolerated. The recommended CS taper is as follows: CS baseline dose will define the rate of tapering (e.g., for doses > 10 and up to 20 mg/day, taper is 2.5 mg every 2 weeks, for CS doses $\leq$ 10 mg/day taper is

2.5 mg every 4 weeks, as clinically tolerated to a goal dose of ≤ 5 mg/day, unless baseline dose is < 5 mg/day). Investigator can modify tapering schedule as per clinical indication however to increase any CS dose, it should meet only disease worsening definition, (see Section 6.8.1.2).

Tapering remains unchanged from Week 20 (Study Day 141) through Week 26 (Study Day 183) (see protocol-specified CS tapering guidance in [Appendix 7](#)). Patients without CS at baseline should maintain immunosuppressants at a stable dose.

For participants who enroll in the OLE period, the CS dose should be tapered as described above to a dose that is clinically tolerated.

IMPORTANT: The Investigator must be familiar with and follow the rules for CS dosage during the study (see details of the CS rules and protocol-specified tapering guidance, in [Appendix 7](#)). If deemed clinically necessary, the Investigator may deviate from the protocol-specified CS tapering rules. Participants may continue study treatment until Week 24 of the DBPC period, followed by the Safety Follow-Up period. Participants do also have the option to participate in the 24-week OLE period.

6.8.1.2 Corticosteroid Rescue Medicine

The following CS rescue rules will apply during the 24-Week DBPC and OLE period:

Control of disease activity/flare with a steroid rescue is allowed only if patient meets disease worsening criteria ([Oddis 2013](#)) at 2 consecutive visits, no less than 2 weeks after the last visit. Disease worsening criteria are defined as meeting at least one of the following:

- Worsening of PGA by ≥ 2 cm on a 10 cm VAS and worsening on MMT-8 by $\geq 20\%$
- Extramuscular Activity Assessment derived from MDAAT worsening by ≥ 2 cm on a 10 cm VAS
- $\geq 30\%$ worsening in any 3 of the 5 IMACS CSM (excluding the CSM “muscle-associated enzymes”; see [Appendix 8](#)).

CS rescue dose as per Investigator’s discretion. See details of the CS rules and guidance in [Appendix 7](#).

Any CS rescue indicates non-responder status. Participants will continue study treatment unless meeting criteria for treatment discontinuation (see Section 7.1).

6.8.2 Permitted Medicines

The only permitted medicines are the following:

1. Any medications required per the medical history and not specifically prohibited by the protocol during the study (i.e., from Screening Visit to the End of the study).
2. COVID-19 vaccines. See Section 2.3.3.

3. Vaccination for influenza virus and *S. pneumoniae* is allowed during Screening, providing that vaccination completes 2 weeks before the Day 1 Visit. Vaccination updates as required according to local guidelines are permitted during the study.
4. CS dose at a maximum of 20 mg/day prednisone equivalent following the CS tapering rules described in Sections 6.8.1 and 6.8.1.2 and [Appendix 7](#)). CS use in non-myositis indications (e.g., asthma, chronic obstructive pulmonary disease, poison ivy, etc.) is permitted except between Weeks 20 to 24. Systemic use of CS (oral/injectable) is allowed up to 10 days for non-myositis conditions (inhaled CS for asthma, chronic obstructive pulmonary disease with requirement for stable dose allowed during the complete study duration).
5. Antimalarial (hydroxychloroquine up to 400 mg/day). If used, to be maintained stable up to Week 24.
6. Permitted SoC therapy during the study for DM and PM including the use of 1 of the following single immunosuppressants or immunomodulators (see [Appendix 6](#) for maximum permitted doses in each case; if used, to be maintained stable up to Week 24):
 - Azathioprine
 - 6-mercaptopurine
 - Mycophenolate (either as mycophenolate mofetil or mycophenolate sodium)
 - Methotrexate
 - Sulfasalazine
 - Leflunomide
 - Cyclosporine
 - Tacrolimus

Note: these medications must be stable throughout the treatment period in addition to the Screening Period, see Section 5.2. For any changes in doses, the Medical Monitor should be contacted, and the changes carefully noted.

Although it is expected participants will be on SoC medications, not all therapies are permitted, as detailed in Section 6.8.3.

7. Vitamin D and calcium supplementation are encouraged per local SoC guidelines. Participants not already taking these medications at Screening should, according to the Investigator's judgment, initiate treatment as soon as possible after Screening. These medications will not be supplied by the Sponsor.
8. Stable dose and regimen of anticoagulants.
9. Treatment with a stable dose of over-the-counter supplements (nonherbal [e.g., iron supplement] is allowed if initiated before the Screening Visit). See Section 6.8.3 and [Appendix 6](#) for prohibited supplements.
10. Analgesics may be used at stable doses or as needed basis for temporary relief of symptoms not due to DM/PM. Any changes in analgesics up to 1 day prior to each study visit that could

affect the assessments (e.g., pain) should be avoided (see Section 6.8.3 and Appendix 6 for prohibited medicines).

- a. Paracetamol (acetaminophen) up to 3 g/day may be initiated or continued for pain control of PM/DM symptoms during the study. This should be titrated off as tolerated.
 - b. Low-dose aspirin (≤ 350 mg/day) for cardiovascular prophylaxis or other indications.
 - c. NSAID may be used as needed for temporary relief of symptoms, avoiding any changes up to 1 day prior to each study visit that could affect assessments (e.g., pain).
11. CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
12. Medications that are sensitive to intestinal BCRP inhibition and administered orally may be used with caution (e.g., rosuvastatin, sulfasalazine). To minimize the risk of DDI via intestinal BCRP inhibition patients may be instructed to administer the concerning medication > 2 hours apart from the study drug administration or may be switched to an alternative, if deemed appropriate.
13. Use of medications known for, or contribute to, the drug induced CCI [REDACTED] should be considered cautiously during the study; a single agent at a stable dose preferably maintained for > 3 months before Day 1 of the study or the lowest effective dose should be considered.
14. Medications associated with QTc interval prolongation should be considered carefully; use may be suspended (switching to an alternative) for the duration of the study if deemed appropriate for the participant.
15. Medications for the treatment of infections and hypersensitivity reactions will be provided at the discretion of the Investigator. If systemic CS are deemed necessary, their use should follow the guidelines in Appendix 7, unless deviation from these guidelines is deemed medically necessary.
16. Sunscreen.

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation.

Caution should be exercised when enpatoran is used concomitantly with other medication if alternative effective treatment option for disease manifestations is limited. The Investigator should use the current product label to assess the benefit-risk profile of any concomitant medicines.

6.8.3 Prohibited Medicines

The following types of medication are not permitted during the study and might lead to discontinuation of study intervention (to be discussed with Medical Monitor on a case-by-case basis); see Appendix 6 for further details on medication guidance and specific prohibited medications:

1. Immunomodulator or immunosuppressant therapies not listed in Section 6.8.2, including but not limited to the following:
 - a. Thalidomide or lenalidomide
 - b. Topical calcineurin inhibitors (e.g., pimecrolimus). Oral tacrolimus up to 0.1 mg/kg is permitted.
 - c. Cyclophosphamide, plasmapheresis, intravenous or subcutaneous Ig
 - d. Alkylating agents (not cyclophosphamide): e.g., chlorambucil
 - e. JAK-STAT pathway inhibitors (e.g., tofacitinib)
 - f. Dapsone
 - g. Retinoids
2. Use of more than 1 medication considered to have immunosuppressant or immunomodulatory properties, not including CS.
3. Exceeding the maximum specified dose for antimalarials or immunomodulators/ immunosuppressants listed in Section 6.8.2 and Appendix 6.
4. Medications associated with CCI [REDACTED] (see Appendix 6). CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Note: for patients on any of these drugs for > 3 months or requiring continuation, use might be permitted if switching to lowest effective dose is considered by the Investigator (in consultation with the prescribing specialist) and discussed with the participant and the Medical Monitor (only allowed for 1 drug).
5. Biologic therapies for PM or DM. Biologic therapies for other indications must be discussed with the Medical Monitor with the exception of insulin or denosumab, which are permitted.
6. Vaccines, included but not limited to live, live attenuated virus vaccine, and excluding influenza, S. pneumoniae and COVID-19 vaccines (see Section 2.3.3). COVID-19 vaccines unauthorized and not approved by the country-specific health agencies or a live or live attenuated virus vaccine are not permitted. See Section 2.3.3.
7. Supplements (herbal/nonherbal/Chinese Medication, e.g., tripterygium, St. John's wort, total glucosides of paeony). Treatment with a stable dose of over-the-counter supplements (nonherbal) is allowed if nonherbal supplements are initiated before the Screening Visit (except for those stated in Appendix 6).
8. Corticosteroids > 20 mg daily prednisone-equivalent for PM and DM. See Appendix 7 for additional CS rules.
9. Topical corticosteroids.
10. Nonsteroidal anti-inflammatory drugs used above maximum prescribed dose per local label.

11. Therapies approved for non-IIM indications (e.g. ravulizumab, efgartigimod). Treatment of lung fibrosis with nintedanib and pirfenidone is permitted.
12. Other investigational agents not specified in this study.

Any medication administered during the study in relation to an increase in myositis disease activity should be discontinued.

Any additional concomitant therapy that becomes necessary during the study and any change to concomitant therapies must be recorded in the corresponding section of the CRF, noting the name, dose, duration, and indication of each drug.

See exclusion criteria (see Section 5.2) for prohibited medication uses before study enrollment.

6.8.4 Other Interventions

Use of potentially excluded procedures such as joint replacement therapy is to be discussed with the Sponsor or designee on a case-by-case basis. Major elective surgeries such as abdominal, thoracic, or joint replacement surgeries should not be planned to occur in the Study Period. Unplanned joint replacement surgery should be discussed at the earliest opportunity prior to the surgery with the Medical Monitor regarding continuation of the participant in the study. Use of prohibited interventions may result in discontinuation of study intervention (see Section 7.1).

A physical therapy-directed exercise regimen for muscle strengthening (i.e., working against resistance, such as bands or light weights) should not be started during the study but is allowed if started ≥ 4 weeks prior to Screening Visit and kept on stable schedule, frequency and extend up to Week 24. Participation in any exercise regimen, and adherence to the regimen, must be documented in the medical records and in the CRF. Other forms of exercise to enhance endurance (aerobics, walking, running) or to increase flexibility (stretching) are allowed.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for ET and Safety Follow-up visit (of DBPC or OLE period, as applicable). The SoA indicates data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

The participant must be withdrawn from study intervention in the event of any of the following:

- Enrollment despite violation of an exclusion criterion which, in the Investigator's and/or Sponsor's opinion, makes discontinuation of the participant necessary.
- Participation in any other interventional study during the duration of this study.
- Occurrence of pregnancy (see Section 8.3.4)

- Occurrence of a clinical condition (e.g., SAE, disease worsening as defined below) for which discontinuation is considered necessary by the Investigator and/or the Sponsor/designee. Disease worsening or flare are defined as one of the following:
 - Worsening of PGA by ≥ 2 cm on a 10 cm VAS and worsening on MMT-8 by $\geq 20\%$ on 2 consecutive visits no less than 2 weeks after the last visit;
 - Extramuscular Activity Assessment derived from MDAAT worsening by ≥ 2 cm on a 10 cm VAS on 2 consecutive visits no less than 2 weeks after the last visit;
 - $\geq 30\%$ worsening in any 3 of the 5 IMACS CSMs on 2 consecutive visits no less than 2 weeks after the last visit (excluding the CSM “muscle-associated enzymes”; see [Appendix 8](#)).

Note: For all criteria, worsening will be determined by comparing to Baseline (Day 1) values (Screening values can be used in case Day 1 values are missing).

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■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

- Occurrence of central nervous system or severe psychiatric AE, i.e., seizure, suicide attempt or ideation, which is assessed to be related to the study intervention.
- Occurrence of severe interstitial lung disease defined as supplemental O₂ required at rest, or FVC of $< 60\%$ predicted.
- Non-compliance to study visits, study intervention etc., judged as significant by the Investigator or Sponsor, e.g., taking $< 80\%$ of the study intervention doses.
- An unplanned event that necessitates discontinuation of study intervention for more than 4 weeks.
- If a participant is unblinded.
- Potentially, due to use of prohibited medication (see [Table 5](#); to be discussed with the Medical Monitor on a case-by-case basis).

If a clinically significant finding is identified (including changes from baseline in QT interval corrected using Fridericia's formula [QTcF]) after start of study intervention, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG at the time of collection will be documented. Any new clinically relevant finding is reported as an AE.

The SoA specifies the data to collect at study intervention discontinuation and follow-up, and any additional evaluations that need to be completed.

7.1.1 Temporary Discontinuation

Study intervention may be stopped at any time at the Investigator's discretion; however, the Medical Monitor must be notified if the participant has missed doses of study intervention for at least 5 consecutive days. The participant will continue their scheduled visits. If the participant's temporary discontinuation is due to an AE, see Section 8. Consultation with the Medical Monitor prior to restarting study medication is advised.

If the participant is unable to resume study intervention, see Section 7.1.

7.2 Participant Discontinuation/Withdrawal from the Study

- When a participant must be withdrawn from the study, the Investigator or designee will inform the Medical Monitor immediately, who will then inform the Sponsor's medically responsible individual (or Medical Responsible).
- A participant may discontinue from the study at any time, at his/her own request or at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- At the time of study discontinuation, if possible, a discontinuation visit will be conducted, as listed in the SoA. The SoA specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.
- If the participant revokes consent for the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed.
- If a participant requests the destruction of any biological samples still remaining, the Investigator will document this in the site study records and inform the Sponsor. The samples will be destroyed.

7.3 Lost to Follow-Up

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

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

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed “lost to follow-up”, the Investigator or designee will make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant’s last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant’s general practitioner or caretaker (where allowed by local regulations) for information. These contact attempts will be documented in the participant’s medical record.
- If the participant continues to be unreachable, he/she will be deemed as “lost to follow-up”.

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA.
- No protocol waivers or exemptions are allowed.
- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations will be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant’s routine medical care, the Investigator will obtain written informed consent as specified in [Appendix 2](#).
- Procedures conducted as part of the participant’s routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded. CCI [REDACTED]
- For study visits where several assessment procedures coincide, vital signs and PROs should first be assessed, then ECG, collection of urine and blood including PK/PD sampling at their specified times, followed by physician assessments, and any remaining procedures. Vital signs and ECG should be performed after at least 5 minutes of rest.
- No more than 75 mL of blood may be drawn in a 24-hour period, and no more than 150 mL of blood in a 4-week period.

Where allowed by local law/regulations, samples collected during this clinical study may be transferred to a biobank and used for future research outside the clinical protocol when additional

consent for this purpose is given. Transfer to the biobank will be documented and any testing of coded biobank samples will **not** be reported in the CSR.

The long-term storage of samples after study completion for future research may be performed with all sample types collected in the study (e.g., PK, CCI, CCI) if the participant consents to optional future medical research.

8.1 Efficacy Assessments and Procedures

Efficacy will be assessed using the instruments and outcomes described below and at the visits specified in [Table 1](#) and [Table 2](#) including baseline visit.

- Efficacy assessments: CDASI, IGA skin activity, MMT-8, CCI, MDAAT, CCI, CCI and muscle-associated enzymes.
- Efficacy assessments informing ACR/EULAR TIS and IMACS DOI are detailed in [Appendix 8](#).
- Patient-Reported Outcome Assessments: PtGA, HAQ-DI, CCI (to assess HRQoL).
- Other patient experience assessments: In-trial qualitative interview.

Details related to efficacy assessments and procedures are summarized in [Appendix 8](#).

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8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings, vital signs, electrocardiograms, occurrence of suicidal behavior and ideation, spirometry or DLCO, and laboratory tests.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in [Section 8.3](#).

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the skin, ear nose and throat, cardiovascular, respiratory, gastrointestinal, and musculoskeletal systems.
- Routine neurological examination, which includes but not limited to assessment of mental status, cranial nerves, reflexes, motor-sensory system, and gait-coordination.

- Additional examination may be performed at the discretion of the Investigator to fully evaluate participant's complaints or AEs.
- Investigators will pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Blood pressure and participant's position; pulse; respiratory rate; temperature and location of measurement, weight, and height (at Screening only) will be measured and recorded. BMI will be determined at Screening and End of Treatment visit only during the DBPC period.
- Blood pressure and pulse measurements will be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones) and measured with an automated device. Manual techniques will be used only if an automated device is not available.

8.2.3 Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically measures heart rate, PR, RR, QRS, QT, and QTcF. Twelve-lead ECG recordings will be obtained after approximately 5 minutes rest in a supine position.
- The parameters and overall evaluation (normal/abnormal) will be recorded in the CRF. Abnormal values judged as clinically significant by the Investigator will be documented on the AE page.
- The printout of the ECG is to be signed, dated, and filed in the Investigator's study file along with a signed and dated copy (if the printouts are not on archive-quality paper). In addition, ECGs will also be stored digitally by the Sponsor.
- ECG tracings collected during the study may be evaluated ad-hoc by the Sponsor.

8.2.4 Clinical Safety Laboratory Assessments

- Blood and urine samples will be collected for the clinical laboratory tests listed in [Appendix 5](#) at the time points listed in the SoA. All samples will be clearly identified and detailed in the Laboratory Manual. No fasting is required for laboratory tests.
- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.
- The tests will be performed by the central laboratory except for ESR, urinalysis and microscopy, HBV DNA test (if required), autoantibody status (if historical data are not available), SARS-CoV-2 (if applicable), T-SPOT (if required), repetition of QuantiFERON (after indeterminate or positive QuantiFERON results that may represent a false positive as assessed by the Investigator), INR (if required), alkaline phosphatase isoenzymes (if alkaline phosphatase is elevated), and urine pregnancy tests (see Section [1.3](#) and [Appendix 5](#)).
- Local laboratory results are only required when central laboratory results are not available in time for study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.

Additionally, if the local laboratory results are used to make a study intervention decision or response evaluation, the results will be recorded in source documentation at the site.

- The Sponsor will receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study will be forwarded to the Sponsor or designated organization.
- The following safety laboratory assessments will be performed at Screening only:
 - FSH and estradiol (for women of nonchildbearing potential only to determine postmenopausal status).
 - Serum pregnancy test (for women of childbearing potential only).
 - Serum virology (Exclusion Criterion 10, Section 5.2).
- Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at monthly intervals during study intervention administration.
- Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at the end of relevant systemic exposure of the study intervention.
- Additional serum or urine pregnancy testing may be conducted at any time during the study to establish the absence of pregnancy, at the Investigator's discretion or if local regulations require them.
- The Investigator will review each laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE, unless it does **not** meet the AE definition, as specified in Appendix 4. The laboratory reports will be filed with the source documents.
- Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded. These include muscle associated enzymes, CCI, and serum cytokines.
- Methods for sample identification during shipping and handling, as well as sampling methods, processing, and storage of samples are detailed in the Laboratory Manual.

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8.2.6 Spirometry or DLCO

Spirometry is a simple test used to help diagnose and monitor certain lung conditions. Spirometry measures include FVC which is the maximum amount of air that can be exhaled when blowing out as fast as possible into a spirometer. Generally, the patient is asked to take the deepest breath they can, and then exhale into the sensor as hard as possible, for as long as possible, preferably at least 6 seconds. It is sometimes directly followed by a rapid inspiration, (inhalation) in particular when assessing possible upper airway obstruction. During the test, soft nose clips may be used to prevent air escaping through the nose.

The DLCO measures the ability of the lungs to transfer carbon monoxide gas from inhaled air to the hemoglobin of red blood cells in pulmonary capillaries. DLCO is reduced in interstitial lung diseases, pulmonary fibrosis due to the thickening of the alveolar-capillary membrane with a restrictive pattern on spirometry. DLCO is most commonly measured using the single-breath technique. The patient takes a full inspiration of a gas mixture containing 0.3 percent carbon monoxide and a tracer gas. After a ten-second breath-hold, the patient exhales. The first portion of the exhaled breath, which is composed of dead-space ventilation, is discarded, and the next liter is collected and analyzed. The difference between the original and final concentrations of carbon monoxide is assumed to represent the gas transported across the lung alveolar surface and to reflect the diffusion capacity.

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

- The definitions of an AE and a SAE are in [Appendix 4](#).
- The Investigator and any qualified designees (e.g., Sub-Investigators) are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The Investigator remains responsible for following up AEs that are serious, or that caused the participant to discontinue the study intervention, as specified in Section 8.3.2.
- Requests for follow-up will usually be made via the Sponsor or CRO-designated study team member, although in exceptional circumstances the global patient safety department may contact the Investigator directly to obtain further information or to discuss the event.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in [Appendix 4](#).

- All AEs and SAEs will be collected from the signing of the ICF until the Safety Follow-up visit at the time points specified in the SoA (Section 1.3). Beyond this reporting period, any new unsolicited SAEs that the Investigator spontaneously reports to the Sponsor will be collected and processed.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance will this exceed 24 hours, as indicated in [Appendix 4](#). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available using the same procedure that was used for the initial report.
- Investigators are not obligated to actively solicit information on AEs or SAEs after the end of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator will promptly notify the Sponsor.

8.3.1 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition.

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

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in [Appendix 4](#).

8.3.2 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AESIs (as defined in Section 8.3.7), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Reasonable attempts to obtain this information will be made and documented. It is also the Investigator's responsibility to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is in [Appendix 4](#).

8.3.3 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE (particularly life-threatening and deaths) is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The

Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

Individual Case Safety Reports will be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.

An Investigator who receives an Individual Case Safety Report describing a SUSAR or other specific safety information (e.g., Emerging Safety Issue Report, summary or listing of SAEs/SUSARs) from the Sponsor will review and file it in the Investigator's Site File and will notify the IRB/IEC, if appropriate according to local requirements.

In this global clinical multicenter study, the Sponsor is in the best position to determine an unanticipated problem (as defined in US Regulations 21 CFR 312.66). The Sponsor will immediately notify all Investigators of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IRB's approval/favorable opinion to continue the study. An unanticipated problem is a serious adverse event that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report, specified in Section 2.3.

8.3.4 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 90 days postintervention contraception described in Section 5.1.
- If a pregnancy is reported, the Investigator will record the pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. Adverse pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered and reported as SAEs. A spontaneous abortion (occurring at < 22 weeks gestational age) or stillbirth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date for a healthy newborn. In case of a congenital anomaly or other illness of the newborn, follow-up will continue until the illness has resolved or there is a definite outcome of the event.
- Any post study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as specified in Section 8.3.3. While the Investigator is not obligated to actively seek this information in former study

participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.5 Cardiovascular and Death Events

Not applicable.

8.3.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.7 Adverse Events of Special Interest

An AESI (a serious or non-serious AEs deemed related to the study intervention) is one of the scientific and medical concern specific to the study intervention, for which ongoing monitoring and prompt communication by the study Investigator to the Sponsor is required. Such AEs of interest may warrant further investigations and in-depth evaluation to better characterize and understand the association between the AE and study intervention.

For this study, AESI(s) include only the following:

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

Upon observation of an AE that qualifies to be an AESI, the Investigator must complete an AESI report Form and communicate the event/s with the Sponsor as described in [Appendix 4](#). AESI classified as serious based on SAE reporting criteria should always be reported as SAE as outlined in Section [8.3.3](#).

8.3.8 Management of Adverse Events (Including AESI)

Standard medical care will be provided at the study site for all AEs occurring during the study in accordance to the institutional guidelines. The severity of AEs will be graded per CTCAE, Version 5.0. The reason for study intervention withdrawal and the nature, duration, and results of any follow-up observations should be recorded in the appropriate section of the CRF.

The study intervention may be interrupted at any time at the Investigator's discretion; however, the Medical Monitor must be notified. Re-initiation of study intervention may occur at the discretion of the Investigator. The following actions should be considered for management of AEs:

Clinical Signs and Symptoms	Proposed Actions
CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
CCI [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]

CTCAE = Common Terminology Criteria for Adverse Events, ECG = electrocardiogram, PE = physical examination.

Asymptomatic Abnormal Laboratory Values	Proposed Actions
Neutrophil count: < 1,000/mm ³ [Grade ≥ 3]	
Platelet count: < 50,000/mm ³ [Grade ≥ 3]	
Lymphocyte count: < 500/mm ³ [Grade ≥ 3]	
- ALT or AST > 8 × ULN if baseline was normal or > 8 × baseline value if baseline was abnormal - ALT or AST > 5 × ULN if baseline was normal or > 5 × baseline value if baseline was abnormal that is persistent over 2 weeks - ALT or AST > 3 × ULN if baseline was normal or > 3 × baseline value if baseline was abnormal and Total Bilirubin > 2 × ULN if baseline was normal and/or INR > 1.5 (INR allowed at local laboratory if above threshold on AST/ALT is met)	

Asymptomatic Abnormal Laboratory Values	Proposed Actions
- ALT or AST $> 3 \times$ ULN if baseline was normal or $> 3 \times$ baseline value if baseline was abnormal and Total Bilirubin $> 2 \times$ baseline value if baseline was abnormal and/or INR > 1.5 (INR allowed at local laboratory if above threshold on AST/ALT is met) - ALT or AST $> 3 \times$ ULN if baseline was normal or $> 3 \times$ baseline value if baseline was abnormal with worsening symptoms (e.g., fatigue, nausea and vomiting, right upper quadrant pain, fever, rash) or eosinophilia	- Temporarily withhold the study intervention. - Clinical evaluation per institutional guidelines. - Repeat the test, preferably within 72 hours but no later than 7 days. - Withhold offending concomitant medication, if appropriate. - Determine alternative contributing factors. - If retest confirms the Grade ≥ 3 toxicity and alternative etiology [confounding factors such as concurrent medications or disease, disease flare or other risk factors] is not confirmed, permanently discontinue the study intervention.
eGFR < 40 mL/min/1.73 m² The eGFR is calculated by the Modification of Diet in Renal Disease equation: $\text{eGFR} = 175 \times (\text{serum creatinine in mg/dL})^{-1.154} \times (\text{age in years})^{-0.203} \times 0.742$ (if female) $\times 1.212$ (if race is black).	Monitor until resolution or return to baseline, non-clinically significant level.
Serum creatinine $> 3.0 \times$ Baseline (Grade ≥ 3)	Study intervention may be re-initiated if retest value returns to baseline or not clinically significant value after discussion with Medical Monitor.

ALT=alanine aminotransferase, AST=aspartate aminotransferase, eGFR=estimated glomerular filtration rate, INR=international normalized ratio, mg/dL=milligrams per deciliter, mL=milliliter, ULN=upper limit of normal.

CCI

1

CCI [REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]

CCI [REDACTED]

[REDACTED]

[REDACTED]
[REDACTED]

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[REDACTED]

[REDACTED]
[REDACTED]

CCI [REDACTED]

8.7 Immunogenicity Assessments

Not applicable.

8.8 Health Economics

Not applicable.

9 Statistical Considerations

9.1 Statistical Hypotheses

No formal statistical hypothesis will be tested, as the study is exploratory.

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CCI

9.3 Analyses Sets

The analysis sets are specified below. The final decision to exclude participants from any analysis set will be made during a blinded data review meeting prior to database lock and unblinding.

Analysis Set	Description
SCR	All participants, who provided informed consent, regardless of the participant's randomization and study intervention status in the study.
FAS	The FAS will include all randomized participants. Participant will be analyzed according to the treatment assigned at randomization as per the Intention-to-Treat principle. This analysis set will be used for efficacy analyses in the DBPC period.
SAF	All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated. This analysis set will be used for safety analyses in the DBPC period.
PK	All participants, who receive at least 1 dose of study intervention, have no important protocol deviations or events affecting PK, and provide at least 1 measurable postdose concentration. Participants will be analyzed per the actual study intervention they received. All PK analyses will be based on this analysis set.
PD	All participants, who receive at least one dose of study intervention, have no clinically important protocol deviations or events affecting PD, and provide at least one measurable PD endpoint postdose. Participants will be analyzed per the actual study intervention they received. All PD analyses will be based on this analysis set.
PD2	All participants (including Screening Failures) who provide at least one measurable sample.
FAS-OLE	All participants, who were administered any dose of study intervention in the OLE period. Analyses will consider participants as randomized in the DBPC period. This analysis set will be used for efficacy analyses in the OLE period.
SAF-OLE	All participants, who were administered any dose of study intervention in the OLE period. Analyses will consider participants as treated in the OLE period. This analysis set will be used for safety in the OLE period.

FAS = Full Analysis Set, FAS-OLE = Full analysis set at OLE period, PD = pharmacodynamic; PK = pharmacokinetic; SAF = Safety Analysis Set, SAF-OLE = Safety Analysis Set at OLE Period, SCR = Screening.

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The following subgroups of the FAS will be considered for primary and secondary efficacy and safety endpoints (assuming there is at least 40% representation per group):

- Participants with rash at baseline: baseline CDASI-A < 14 , or ≥ 14
- All participants: baseline MMT-8 ≥ 80 to 136, or > 136
- DM vs PM (as stratified as defined per 2017 ACR/EULAR classification criteria)

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

FAS/FAS-OLE will be the analysis set for all efficacy analyses in the DBPC/OLE.

Descriptive statistics on the TIS and other endpoints will be provided by treatment group and visit. TIS will be derived as per [Aggarwal 2017](#). No imputation of missing values will be done.

Reference #	Category	Statistical Analysis
Primary		
1 – TIS	Main	Descriptive statistics on the TIS will be provided by treatment group and visit. Means for the TIS and corresponding 95% CIs will be presented by treatment group and visit. Similarly, the mean differences (and 95% CI) between enpatoran and placebo will be provided at each visit. 95% CIs will be based on parametric (t-test) or non-parametric test. Details will be provided in the IAP.
	Supportive	Modeling of TIS with CS dose using actual time and accounting for covariates will be performed (will be specified in the IAP). Covariates include PM/DM, disease severity and other important patient characteristics.
Secondary		
3 – TIS ≥ 20 , ≥ 40 , and ≥ 60	Main	Descriptive statistics on the occurrence of TIS ≥ 20 , ≥ 40 , and ≥ 60 response will be provided by treatment group and visit. Differences between enpatoran and placebo will be presented. The corresponding 95% CIs will be based on Miettinen and Nurminen method (Miettinen and Nurminen, 1985). Intercurrent event will be considered non-responder.
4	Main	TIS at each visit from Week 4 up to and including Week 24 and each of the TIS components. Means for the TIS and corresponding 95% CIs will be presented by treatment group and visit.
5	Main	IMACS responder. Descriptive statistics on the occurrence of IMACS response will be provided by treatment group and visit. Intercurrent event will be considered non-responder.
6	Main	Change and percent change from baseline in CDASI-A/D and IGA skin activity at each visit from Week 4, up to Week 24. Means for the endpoint and corresponding 95% CIs will be presented by treatment group and visit.

Reference #	Category	Statistical Analysis
CCI		

CDASI = cutaneous dermatomyositis area and severity index, CS = corticosteroids, DM = dermatomyositis, IAP = integrated analysis plan, IGA = Investigator's Global, IMACS = International Myositis Assessment and Clinical Studies, PM = polymyositis, TIS = Total Improvement Score.

9.4.2 Safety Analyses

All safety analyses will be performed on the SAF for the DPBC period and SAF-OLE for the OLE period.

Estimand reference #	Category	Statistical Analysis Methods
Primary		
2 (DBPC period)	Adverse Events	Descriptive statistics, AESI summaries
	Clinical Laboratory Test Values	Descriptive statistics, shift tables, boxplots, individual participant line plots, eDISH figures
	ECG Parameters	Descriptive statistics
	Vital Signs	Descriptive statistics
Secondary		
7 (OLE period)	Adverse Events	Descriptive statistics, AESI summaries
	Clinical Laboratory Test Values	Descriptive statistics, shift tables, boxplots, individual participant line plots, eDISH figures
	ECG Parameters	Descriptive statistics
	Vital Signs	Descriptive statistics
Tertiary/ Exploratory	Not applicable	Not applicable

AESI = adverse event of special interest, DBPC = Double-Blind Placebo-Controlled, ECG = electrocardiogram, eDISH = evaluation of drug-induced serious hepatotoxicity, OLE = Open Label Extension.

9.4.3 Other Analyses

Details on the PK, PD and CCI CCI analyses will be in the Integrated Analysis Plan that will be finalized before database lock. CCI

CCI clinical efficacy and safety endpoints, will be described in a separate pharmacometrics analysis plan and presented separately from the main CSR.

9.4.4 Sequence of Analyses

Study team will be blinded until the DBPC period is completed at which time full analysis will be performed (DBPC analysis, Week 24). A second analysis will be performed after the OLE part is

completed (OLE analysis, Weeks 48 to 50 [allowing for potential 2-week period between DBPC and OLE]). Details will be provided in the integrated analysis plan.

Analyses will be performed at regular intervals for the purpose of safety monitoring by the IDMC and, based on its review, the IDMC will make recommendations regarding study modification, continuation or termination. An ad-hoc benefit-risk assessment may be conducted to inform Sponsor's decision making on the clinical development program of enpatoran. Criteria for conducting this analysis include but are not limited to slower than anticipated recruitment of patients in the trial or emerging evidence from other clinical trials or published literature. Timing and content of the interim analysis will be described in the IDMC charter, an interim analysis Firewall charter and related documentation. To maintain study integrity, the IDMC and an internal Firewall Team (not the study team) will convene and evaluate the data as described in the IDMC charter and the Firewall charter that will document the full membership, mandate, and processes of the IDMC and the Firewall Team. Participants and site personnel will remain blinded until the end of the study.

10 References

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11 Appendices

Appendix 1 Abbreviations

Ab	antibody
ACR/EULAR	American College of Rheumatology/European League Against Rheumatism
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
CCI	
AST	aspartate aminotransferase
ASyS	anti-synthetase syndrome
AUC	Area under curve
BCRP	breast cancer resistance protein
BMI	body mass index
CDASI	cutaneous dermatomyositis area and severity index
CIOMS	Council for International Organizations of Medical Sciences
CLE	cutaneous lupus erythematosus
C _{max}	maximum concentration
C _{max,ss}	maximum concentration at steady state
C _{min,ss}	trough concentrations at steady-state
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	clinical research organization
CS	corticosteroids
CSM	core set measures
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
C _{trough}	the concentration observed at the end of a dosing interval immediately before next dosing
DBPC	double-blind placebo controlled
DLCO	diffusing capacity for carbon monoxide
DM	dermatomyositis
DNA	deoxyribonucleic acid
DOI	definition of improvement
ECG	electrocardiogram
ESR	erythrocyte sedimentation rate
EudraCT	European Clinical Trials Database
FAS	full analysis set
FAS-OLE	full analysis set at OLE period
FIH	first in humans
FSH	follicle-stimulating hormone
FVC	forced vital capacity

GCP	good clinical practice
HAQ-DI	health assessment questionnaire-disability index
HBV	hepatitis B virus
HCV	hepatitis C virus
CCI	
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HMGCR	3-hydroxy-3-methylglutaryl-coenzyme A reductase
HRQoL	health-related quality of life
HRT	hormonal replacement therapy
IB	investigator's brochure
IBM	inclusion body myositis
ICF	informed consent form
ICH	international council for harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
IFN	interferon
CCI	
Ig	immunoglobulins
IIM	idiopathic inflammatory myopathies
IMACS	International Myositis Assessment and Clinical Studies
IMNM	immune mediated necrotizing myopathy
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
JAK-STAT	Janus Kinase-Signal Transducer and Activator of Transcription
LTBI	latent tuberculosis infection
MDAAT	myositis disease activity assessment tool
MMT	manual muscle testing
MRI	magnetic resonance imaging
NF-κB	nuclear factor-kappa B
NSAID	non-steroidal anti-inflammatory drug
OLE	open label extension
OTC	over the counter
PD	pharmacodynamic
PGA	Physician Global Activity
PK	pharmacokinetic
PM	polymyositis
PRO	patient reported outcome
PtGA	Patient Global Activity
QoL	quality of life
QTcF	corrected QT interval by Fridericia' formula

RNA	ribonucleic acid
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAF	safety analysis set
SAF-OLE	safety analysis set at OLE Period
CCI	
SLE	systemic lupus erythematosus
SoA	schedule of activities
SoC	standard of care
SRC	safety review committee
SRP	signal recognition particle antibody
SSC	study steering committee
SUSAR	suspected unexpected serious adverse reactions
TB	tuberculosis
TEAE	treatment-emergent adverse event
TIS	total improvement score
TLR	toll-like receptor
TNF	tumor necrosis factor
ULN	upper limit of normal
VAS	visual analogue scale
WOCBP	woman of childbearing potential

Appendix 2 Study Governance

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative (where allowed by local laws and regulations) and answer all questions on the study.
- Participants will be informed that their participation is voluntary.
- Participants or their legally authorized representative (where allowed by local laws and regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; HIPAA requirements, where applicable; and the IRB/IEC or study center.
- The medical record will include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent will also sign the ICF.
- If the ICF is updated during their participation in the study, participants will be reconsented to the most current, approved version.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor will inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure will also be explained to the participant and pregnant partners (if applicable), who will be required to give consent for their data to be used, as specified in the informed consent.
- The participant will be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative

- The study will be conducted at approximately 37 sites in approximately 11 countries in an outpatient basis.

- The Coordinating Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Coordinating Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report.
- Special oversight committees will include IDMC, SSC, IIM expert committee, and internal Firewall team.
- An IDMC will review unblinded study information to assess safety and tolerability during the conduct of the study and, based on its review, make recommendations regarding study modification, continuation, or termination. The IDMC will be a group of independent experts external to the study. If needed, the IDMC will also perform an ad-hoc benefit-risk assessment. The full membership, mandate, and processes of the IDMC will be provided in the IDMC charter.
- Study Steering Committee (SSC) will ensure that the study meets scientific standards and provide direction and oversight to the study from an Investigator's perspective, including protocol creation and amendments, study execution, and evaluation of study results at the end of study. Investigators in this clinical study and other experts who are not otherwise involved in the trial may serve on this committee.
- An idiopathic inflammatory myopathies (IIM) expert committee may be responsible for confirming the eligibility of participants, in case of doubts by eligibility team (Sponsor or designee, including Medical Monitor) or in cases with diagnosis of (non-active) concurrent connective tissue disease(s). Clinical presentation of active myositis may also be confirmed by IIM expert committee based on the adjudication form. The expert committee will include up to 2 external IIM experts. The experts will review patient data and may request additional data from Investigators. If the external expert is also an Investigator, she/he may not adjudicate their own patient.
- The Firewall Team will be comprised of relevant Sponsor senior experts (as described in a dedicated Firewall charter), who are independent of the study team, to review unblinded data based on ad-hoc benefit-risk assessment.
- IQVIA and Accelsiors will provide CRO services and Q2 solutions will serve as central laboratory.
- Sponsor will be responsible for supply and manufacture of study intervention (enpatoran and placebo).

Details of structures and associated procedures will be defined in a separate Study Reference Manual.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
 - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines
 - Applicable ICH GCP Guidelines

- For studies with EU member states sites, with Regulation [EU] No 536/2014 Applicable laws and regulations
- The protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) will be submitted to an IRB/IEC for review and approve before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).
- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.
- When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor (or designee) physician. This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor (or designee) physician to assist with the medical emergency and to provide support for the potential unblinding of the participant concerned.

Clinical Study Insurance and Compensation to Participants

- Insurance coverage will be provided for each country participating in the study. Insurance conditions will meet good local standards, as applicable.

Clinical Study Report

- After study completion, the Sponsor will write a clinical study report in consultation with the Coordinating Investigator, or other relevant study-appointed committees or groups.

Publication

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.

- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- After completion of the study, a CSR will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3 and will be submitted in accordance with local regulations.
- Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere should be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third-party except to such of the Investigator's employees and staff who had been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than for determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.
- The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study intervention and therefore may be disclosed as required to other clinical Investigators, to the USA Food and Drug Administration, and to other government agencies. The Investigator also understands that, to allow for the use of the information derived from the clinical study, the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study.
- No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement
- The first publication will include the results of the analysis of at least the primary endpoints and will include data from the study site. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission. The Sponsor will not suppress publication but maintain the right to delay publication to protect intellectual property rights.
- A summary of study results will be provided if required by local regulations (e.g., Regulation [EU] No 536/2014). It should be noted that in this multicountry study provision of such summary may occur > 1 year after end of clinical study was notified in an individual country (including any or all EU member states). Due to the study's sample size, it is considered justified to await completion in all countries and provide a summary of study results within 1 year from global end of clinical study, rather than providing summary results based on partial information.
- Posting of data on www.ClinicalTrials.gov is planned and will occur 12 months after the last visit, or scheduled procedure, or another appropriate date to meet applicable requirements.

Data Quality Assurance

- All participant study data will be recorded on printed or electronic CRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the Study Reference Manual.
- For PRO data (e.g., QoL and pain assessments), ePRO will be used.
- The Investigator will maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator will permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- QTLs will be predefined in the Quality Risk Management Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. Details will be outlined in Data Management documents and procedures.
- Study Monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- The Investigator will retain records and documents, including signed ICFs, pertaining to the conduct of this study for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.
 - The archiving period is 25 years in EU member states.
- For studies with EU member states sites, the data will be collected and processed in accordance with Directive 95/46/EC.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The source data verification process is described in a separate manual.

- The Investigator will maintain source documents that support the data recorded in the CRFs.
- Data recorded on CRFs that are transcribed from source documents will be consistent with the source documents or the discrepancies will be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records will be available.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in the CRF guidelines.

Study and Site Start and Closure

The study start date is when the first participant signs the Informed Consent Form.

Study and Site Closure

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

Reasons for the early closure of a study site by the Sponsor or Investigator may include:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further development of the Sponsor's compound
- If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any third-party service providers of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

Appendix 3 Contraception and Barrier Requirements

WOCBP:

A woman is of childbearing potential (fertile) following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

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

Postmenopause:

Postmenopause is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
- A female on HRT and whose menopausal status are in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization:

For this study, permanent sterilization includes:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Documentation can come from the site personnel's review of the individual's medical records, medical examination, or medical history interview.

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), Investigator discretion applies to determine study entry.

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a WOCBP, and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
 - Oral
 - Intravaginal
 - Transdermal
 - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation
 - Oral
 - Injectable
- Sexual abstinence: a highly effective method only if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Notes:

Contraceptive use by men or women is consistent with local regulations on the use of contraceptive methods for clinical study participants.

Highly effective methods are those with a failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

Acceptable methods are considered effective, but not highly effective (i.e., have a failure rate of $\geq 1\%$ per year). If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are **not** acceptable methods of contraception for this study. Male condom and female condom cannot be used together (due to risk of failure from friction).

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether considered related to the study intervention or not. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline and are judged to be more severe than expected for the participant's condition are considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease, but may be leading to study intervention discontinuation). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or a SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or a SAE if they fulfil the definition of an AE or SAE.
Events <u>NOT</u> Meeting the AE Definition
• Unless judged by the Investigator to be more severe than expected for the participant's condition, any clinically significant abnormal laboratory findings, other abnormal safety assessments that are associated with the underlying disease, the disease/disorder being studied within the expectedness for participant's condition, as judged by the Investigator. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Other Adverse Events to be Reported Using a Specialized Procedure or Form

- All pregnancies occurring during the study and their outcome will be documented on the Pregnancy report form and Parent-Child/Fetus Adverse Event Report form as outlined in Section 8.3.4.
- The following procedures should be followed for report overdoses (refer to CRF guidelines for further details):
 - Overdoses without an AE should be reported using the paper SAE Overdose Report form only, stating if the overdose was accidental or intentional.
 - Overdoses associated with a non-serious AE must be recorded on the AE CRF and also the paper SAE Overdose Report form. Overdoses associated with a SAE must be recorded on the AE CRF and the paper SAE Report form.

SAE Definition

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE will be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. • However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization must be documented and reported as SAEs.

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is **not** intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations

- Medical or scientific judgment will be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events are usually considered as serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Any suspected transmission of an infectious agent via a study intervention is also considered an SAE for reporting purposes, as specified below for reporting SAEs or AESIs.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- As needed, Sponsor/designee may ask for copies of certain medical records (e.g., autopsy reports, supplemental lab reports, documents on medical history/concomitant medications, discharge letters), as supporting source documentation. All participant identifiers, except the participant number, will be redacted on these copies before submission to Sponsor/designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- Specific guidance is in the CRF Completion and Monitoring Conventions.

Assessment of Intensity

The Investigator will assess the intensity of each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. Do not confuse an AE that is assessed as severe with a SAE. Severe is a category used to rate the intensity of an event; both AEs and SAEs can be assessed as severe.

An event is defined as “serious” when it meets at least 1 of the predefined criteria specified in the definition of an SAE, NOT when it is rated as severe.

If death occurs, the primary cause of death or event leading to death will be recorded and reported as an SAE. “Fatal” will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (e.g., sudden death, unexplained death), the death per se might then be reported as an SAE.

Assessment of Causality

- The Investigator will assess the relationship between study intervention and each AE/SAE occurrence:
 - Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention. A reasonable alternative explanation will be available.
 - Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator will document in the medical notes that he/she has reviewed the AE/SAE and assessed causality.

- There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or its designee. To meet the reporting timeline, the causality assessment is not required for the initial report.
- The Investigator may change his/her causality assessment after considering follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by Sponsor/designee to elucidate the nature and/or causality of the AE or SAE, as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Sponsor/designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting by an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE in multicenter studies to the Sponsor or its designee will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE form, specified below, to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the Sponsor's safety department.
- By exception, an SAE (or follow-up information) may be reported by telephone. The site will complete the electronic SAE data entry immediately thereafter.

SAE Reporting by a Paper Form

- SAE reporting on a paper report form may be used in single center studies in addition to the standard electronic CRF and as a back-up method for an EDC system failure. The form includes completion instructions for the Investigator, names, addresses, and telephone and fax numbers. All information from the paper form will be transcribed into the electronic form as soon as the system becomes available.
- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the form within 24 hours after becoming aware of the event.
- Additional documents (e.g., laboratory reports, autopsy report, hospital discharge letter) and relevant pages from the CRF may be required in addition (e.g., medical history, concomitant medication). The data provided will be consistent with the information in the CRF.

Reporting of AESIs

- For a non-serious AESI, the site will complete the specific AESI report form and notify the Sponsor immediately (within 24 hours), using the same process for reporting SAEs, as specified above.
- For a serious AESI, the site will complete an SAE report form, using the SAE reporting process, specified above.

Reporting of Pregnancies

- Pregnancy will be reported whether related to the study intervention using the applicable paper form.
- The applicable form will be used to report if an abnormal outcome of the pregnancy occurs and the child/fetus sustains an event.
- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.

Appendix 5 Clinical Laboratory Tests

The protocol-required clinical laboratory assessments are in the following table:

All study-required laboratory assessments will be performed by a central laboratory, except for ESR, urinalysis and microscopy, HBV DNA test (if required), autoantibody status (if historical data are not available), SARS-CoV-2 (if applicable), T-SPOT (if required), repetition of QuantiFERON (after indeterminate or positive QuantiFERON results that may represent a false positive as assessed by the Investigator), INR, alkaline phosphatase isoenzymes (if alkaline phosphatase is elevated), and urine pregnancy tests.

Laboratory Assessments	Parameters			
Hematology	RBC count Platelet count Reticulocytes (absolute count)		MCV	White Blood Cell Count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	Hemoglobin		MCH	
	Hematocrit			
	ESR ¹			
Biochemistry ² (including muscle-associated enzymes)	Blood Urea Nitrogen	Potassium	Aspartate aminotransferase ^{4,5}	Total Bilirubin
	Creatinine	Sodium	Alanine aminotransferase ^{4,5}	Total Protein
	Glucose	Calcium	Alkaline phosphatase	eGFR ³
	Lactate Dehydrogenase ⁴	Creatinine Kinase ⁴	Gamma Glutamyl Transferase	Albumin
	Aldolase ⁴	C Reactive Protein		
CCI				
Notes: ¹ ESR is to be performed as part of hepatic assessment (<i>when AST/ALT >2 times UNL</i>) or when HBV DNA is detectable. ² If alkaline phosphatase is elevated, consider measuring the alkaline phosphatase isoenzymes. ³ Calculated by the Modification of Diet in Renal Disease equation by the central laboratory ⁴ Muscle-associated enzymes ⁵ INR may be checked locally when ALT or AST > 3 × ULN if baseline was normal or > 3 × baseline value if baseline was abnormal				
Routine Urinalysis	- Specific gravity - pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick - Microscopic examination (if blood, protein, leukocyte or cast is abnormal).			
Other Screening Tests	- Follicle Stimulating Hormone and estradiol (for non-WOCBP only). - Highly sensitive urine hCG pregnancy test (as needed for a WOCBP). Note: urine testing at a local laboratory will be standard for the protocol. If required by local regulations or the IRB/IEC, serum testing will be done instead. - Serology: hepatitis B (HBs antigen, HBsAb, HBcAb with reflexive HBV DNA) and hepatitis C (HCVAb and reflexive HCV RNA), per exclusion criteria. - HIV laboratory test (either antibody or NAAT).			

Laboratory Assessments	Parameters
	Tuberculosis assessment (QuantiFERON, T-SPOT).
Pregnancy test after Screening.	Urine pregnancy test (or a serum test if required by local regulation or the IRB/IEC).
Other tests	
SARS-CoV-2 test	Only if applicable (See Sections 5.2 and 8.2.4)
HBV DNA after Screening	Only required during study for participants who at Screening were positive for anti-HBc antibody and/or anti-HBs antibody with non-detectable HBV DNA.

MCV = mean corpuscular volume, ALT = alanine aminotransferase, AST = aspartate aminotransferase, eGFR = estimated glomerular filtration rate, ESR = erythrocyte sedimentation rate, HBcAb = Hepatitis B core antibody, HBs = Hepatitis B, HBsAb = Hepatitis B surface antibody, HBV = Hepatitis B Virus, HCG = human chorionic gonadotropin, HCV = hepatitis C virus, HCVAb = Hepatitis C virus antibodies, HIV = Human Immunodeficiency Virus, IEC = independent ethics committee, INR = international normalized ratio, IRB = institutional review board, MCH = mean corpuscular hemoglobin, NAAT = nucleic acid amplification tests, pH = potential hydrogen, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, red blood cell = RBC; ULN = upper limit of normal, WOCBP = women of childbearing potential.

Table 5 Prohibited Medications With Required Washout

Medication Type	Medications	Discontinuation (weeks) before Day 1
CS	> 20 mg daily prednisone-equivalent (any dosage form)	4 ^a
	Intramuscular or injectable CS (intralesional therapies to be stopped 2 weeks prior to Day 1) ^a	4 ^a
	Topical CS Class	2 ^a
NSAIDs	Above maximum prescribed dose per local label	2 ^a
CCI		
Immunomodulators/ Immunosuppressants ^b	Thalidomide or lenalidomide	4
	Calcineurin inhibitors: topical use > 1 time per day (e.g., pimecrolimus). Oral tacrolimus up to 0.1 mg/kg is permitted.	2 ^a
	Cyclophosphamide	12
	Plasmapheresis	
	Alkylating agents (not cyclophosphamide): e.g., chlorambucil	24
	Dapsone, or retinoids	8
	JAK-STAT pathway inhibitors (e.g. tofacitinib)	4
	Biologic therapies	Abatacept
Anti-TNF α (e.g. etanercept, adalimumab)		12
Intravenous or subcutaneous Ig (8 weeks wash-out if only $\leq$ 2 doses received)		
Belimumab		16
Anti-IFN (e.g. anifrolumab)		
Anti-IL-6 receptor (tocilizumab, sarilumab) or anti-IL-6 (siltuximab)		24
B cell depleting/modulating therapy such as anti-CD20 agents (e.g. rituximab, telitacicept, atacicept) or dual or other anti-B Lymphocyte Stimulator/proliferation inducing ligand neutralizing therapies (exception belimumab: see above)		24
IL-12/IL-23 inhibitor: e.g., ustekinumab		24

Medication Type	Medications	Discontinuation (weeks) before Day 1
Vaccination ^c	Anti-IL-1 agents	24
	Included but not limited to subunit or inactivated vaccines	2
	Live or live attenuated virus vaccine	4
Supplements (Herbal/nonherbal/Chinese medication)	Tryptophan ^d	2 weeks or 5 half-lives, whichever is longer
	Tripterygium, total glucosides of paeony	4
Antidepressants	██████████ CCI ██████████ ██████████ tricyclic antidepressants ^d , monoamine oxidase inhibitors ^d , lithium ^d .	2 weeks or 5 half-lives, whichever is longer
Anxiolytic	Buspirone ^d	2 weeks or 5 half-lives, whichever is longer
Analgesics	Tramadol, pethidine ^d , fentanyl ^d , dextromethorphan ^d (e.g., in OTC cough remedies)	2 weeks or 5 half-lives, whichever is longer
██████████	CCI ██████████	2 weeks or 5 half-lives, whichever is longer Occasional use for no more than 1 to 2 days treatment as per label dosage is allowed
Antibiotics	Linezolid ^d , tedizolid ^d	2 weeks or 5 half-lives, whichever is longer
Investigational agents	BTK inhibitors (e.g. ibrutinib) Other immunosuppressants (e.g. nipocalimab, daxdilimab)	12 weeks or 5 half-lives, or as per washout requirement from the previous protocol, whichever is longer
CCI ██████████ ██████████	██████████ ██████████ ██████████ ██████████ ██████████ ██████████ ██████████ ██████████ ██████████	Replacement by another drug to be considered before study entry CCI ██████████ ██████████ ██████████ ██████████
Treatments approved only for non-IIM indications	E.g. ravulizumab, efgartigimod. Treatment of lung fibrosis with nintedanib and pirfenidone is permitted.	12 weeks or 5 half-lives, whichever is longer
Other	Methylthioninium chloride (methylene75 blue) ^d	2 weeks or 5 half-lives, whichever is longer
Any medication administered during the study and related to an increase in PM/DM disease activity	NSAID	During the study: may be used only as needed for temporary relief of symptoms. Any changes in NSAIDs up to 1 day prior to each study visit that could affect assessments should be avoided.

d For patients on any of these drugs for > 3 months or requiring continuation, use might be permitted if switching to lowest effective dose is considered by the Investigator (in consultation with the prescribing specialist) and discussed with the participant and the Medical Monitor (only allowed for 1 drug). Drugs under this category with CCI potential need to be discussed with Medical Monitor.

Table 6 **Medications with Required Duration of Stable Dose**

[illegible]

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Category	Item	Value
Category 1	Item 1.1	100
	Item 1.2	200
	Item 1.3	300
	Item 1.4	400
Category 2	Item 2.1	500
	Item 2.2	600
	Item 2.3	700
Category 3	Item 3.1	800
	Item 3.2	900

[illegible]

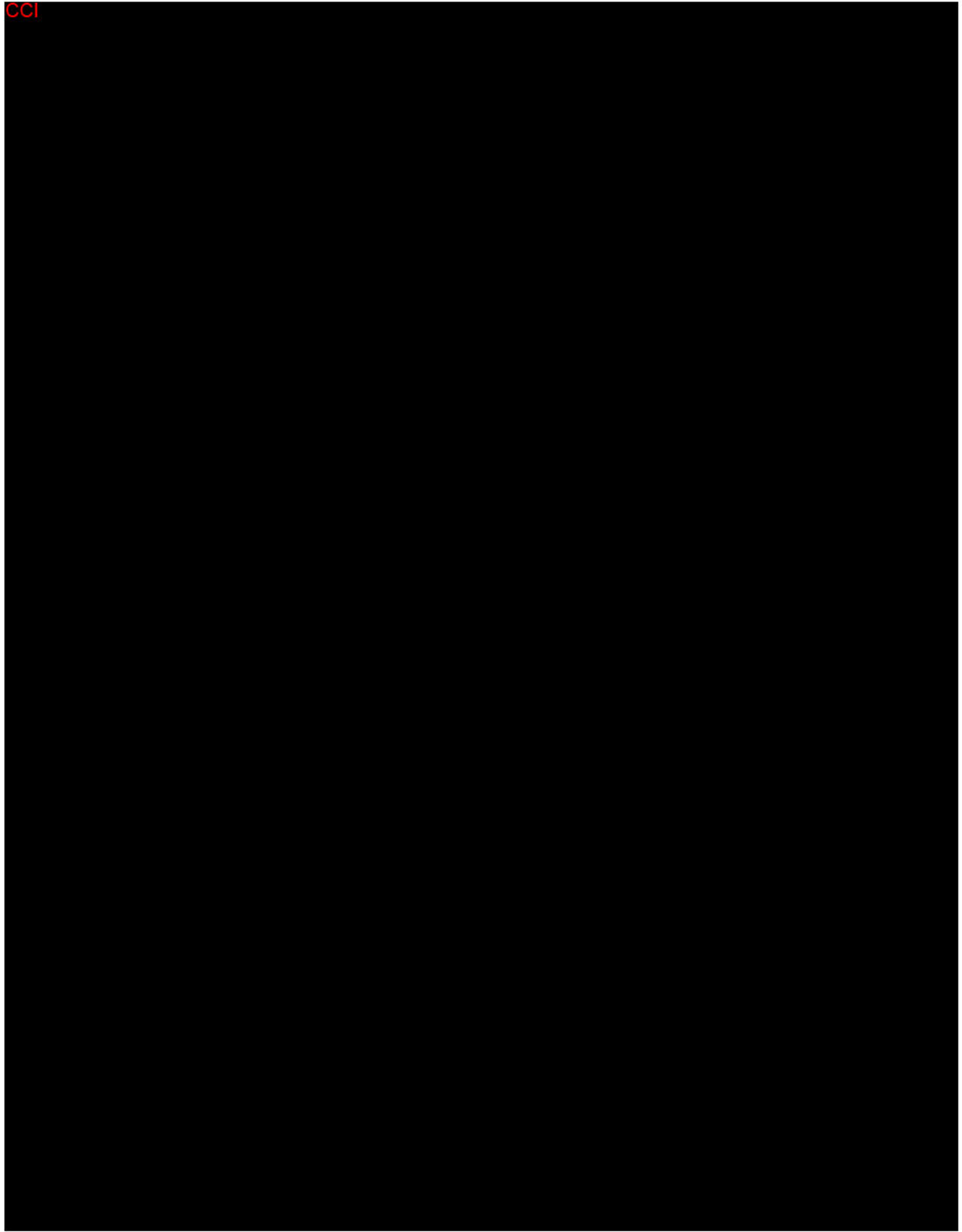
	(b) (6), (b) (7)(C)	(b) (6), (b) (7)(C)
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[REDACTED]

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-
- | Age Group | Percentage of Respondents |
|--------------|---------------------------|
| 18-29 | 80% |
| 30-49 | 75% |
| 50-64 | 65% |
| 65 and older | 55% |

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Appendix 8 Efficacy and Patient-Reported Outcome Assessments and Procedures

See [Table 1](#) for the study population and frequency for each assessment and procedure.

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS ([Posner 2007](#)) assesses the suicidal behavior and suicidal ideation in participants. Occurrence of suicidal behavior after randomization is defined as having answered “yes” to at least 1 of the 4 suicidal behavior subcategories (actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior). Occurrence of suicidal ideation after randomization is defined as having answered “yes” to at least 1 of the suicidal ideation sub-categories (wish to be dead, nonspecific active suicidal thoughts, active suicidal ideation with any methods [not plan] without intent to act, active suicidal ideation with some intent to act [without specific plan], and active suicidal ideation with specific plan and intent).

Rationale

The C-SSRS is a low burden tool designed to track suicidal AEs throughout any intervention study and is considered to be the “gold standard” for assessment. This scale is administered by the clinician or trained designee during the Screening Visit. The measure succinctly covers the full spectrum of suicidality addressing both behavior and ideation and is now strongly recommended by the US FDA in clinical studies. It is the prospective version of the Columbia suicide classification system commissioned by the FDA, which provided the data for their safety analyses, and is used across numerous industry and National Institutes of Mental Health-sponsored studies.

Assessments

The C-SSRS is a unique and simple method of assessing both behavior and ideation that tracks all suicidal events and provides a summary of suicidality. It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation and deterrents), all of which are significantly predictive of completed suicide.

The C-SSRS will be performed at the visits specified in [Section 1.3](#). The trained rater will record the clinical observation on the scale which will be used as the source document.

Patients who answer “yes” to any suicidal behavior questions or to suicidal ideation questions 4 or 5 on the C-SSRS, patient is to be excluded and should be referred for appropriate psychiatric care and the Medical Monitor notified.

Patient’s Global Activity (PtGA)

PtGA is an IMACS Core Set Measure used in the calculation of the IMACS DOI and ACR/EULAR TIS. It consists of a 10 cm VAS assessing the overall activity of the patient’s disease today from 0 cm (“No evidence of disease activity”) to 10 cm (“Extremely active or severe disease activity”), disease activity being active inflammation in the patient’s muscles, skin, joints, intestines, heart, lungs or other parts of the body, which can improve when treated with medicines.

Health Assessment Questionnaire -Disability Index (HAQ-DI)

HAQ-DI is an IMACS Core Set Measure used in the calculation of the IMACS DOI and ACR/EULAR TIS. It is a generic rather than a disease-specific instrument comprised of 8 sections (dressing, arising, eating, walking, hygiene, reach, grip, and activities), with 2 to 3 questions per section. Scoring within each section is from 0 (without any difficulty) to 3 (unable to do). For each section the score given to that section is the worst score within the section. The 8 scores of the 8 sections are summed and divided by 8.

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Cutaneous Dermatomyositis Area and Severity Index (CDASI)

CDASI is a clinician-scored single page instrument that separately measures activity and damage in the skin of DM patients. CDASI has 3 activity measures (CDASI-A: erythema, scale, and erosion/ulceration) and 2 damage measures (CDASI-D: poikiloderma and calcinosis) which are assessed over 15 body areas. In addition, Gottron's papules on the hands, periungual changes and alopecia are evaluated separately both for activity and damage. Activity and Damage Subscale scores range from 0 to 100 and 0 to 32, respectively, where higher scores indicate greater disease severity.

Investigator's Global Assessment (IGA) Skin Activity

The IGA skin activity is a five-point score that defines the level of disease severity based on overall lesion characteristics where 0 is "clear" and "4" is severe.

International Myositis Assessment and Clinical Studies (IMACS)

American College of Rheumatology/European League Against Rheumatism Total Improvement Score (ACR/EULAR TIS)

The ACR/EULAR TIS is derived from the evaluation of the results from 6 CSM of myositis disease activity established for clinical trials in patients with DM and PM. These CSM were validated by the IMACS. A total improvement score is determined by summing scores for each CSM, based on improvement in (absolute percent change) $[\text{final value} - \text{baseline value}] / \text{range} \times 100$ and relative weight of each core set measure. The TIS scale ranges from 0 to 100 with thresholds for minimal (≥ 20), moderate (≥ 40) and major (≥ 60) improvement in the combined 6 CSM. Refer to [Aggarwal 2017](#) for details on IMACS TIS.

IMACS Core Set Measures (CSM) and Ranges

Table 10 IMACS Core Set Measures

Core Set Domain	Core Set Measures	Range
PGA ^a	PGA VAS	0-10
PtGA	PtGA VAS	0-10
Muscle strength	MMT-8 (composite score of 8 muscle groups tested bilaterally)	0-150
Physical function	HAQ-DI	0-3
Muscle-associated enzymes ^b	Most abnormal muscle-associated enzyme among CK, LDH, AST, ALT, Aldolase	Depends on ULN laboratory range of enzymes ^c
Extramuscular Activity Assessment ^a	Extramuscular portion of the MDAAT VAS: constitutional, cutaneous, arthritis, GI, pulmonary, cardiac	0-10

Source: [Rider 2004](#).

VAS presented as a 10 cm scale.

ALT=aspartate aminotransferase, AST=aspartate aminotransferase, CK=creatine kinase, CSM=core set measures, GI=gastrointestinal HAQ-DI=Health Assessment Questionnaire-Disability Index; LDH=lactate dehydrogenase, MDAAT=Myositis Disease Activity Assessment Tool, MMT=Manual Muscle Testing, PGA= Physician Global Activity, PtGA=Patient Global Activity, ULN=upper limit of normal, VAS=Visual Analog Scale.

a Derived using the MDAAT.

b The current study does not consider this CSM for definition of disease worsening or flare definition.

c The ULN is determined according to the individual laboratories in the participating centers.

In the current study, disease worsening or flare are defined as one of the following on 2 consecutive visits no less than 2 weeks after the last visit:

- Worsening of PGA by ≥ 2 cm on a 10 cm VAS and worsening on MMT-8 by $\geq 20\%$;
- Extramuscular Activity Assessment derived from MDAAT worsening by ≥ 2 cm on a 10 cm VAS;
- $\geq 30\%$ worsening in any 3 of the 5 IMACS CSMs (excluding the CSM muscle-associated enzymes).

International Myositis Assessment and Clinical Studies - Definition of Improvement (IMACS DOI)

The IMACS DOI are response criteria for adult DM/PM that were developed and partially validated by IMACS. However, these criteria were not prospectively validated and have some limitations, therefore they are considered preliminary. The criteria use the IMACS CSM and are based on at least 20% improvement in 3 of 6 CSM, with no more than 2 CSM worsening by at least 25% (which cannot be muscle strength). Refer to [Rider 2004](#) for details on IMACS DOI.

Manual Muscle Testing-8 (MMT-8)

MMT-8 is an IMACS Core Set Measure used in the calculation of the IMACS DOI and ACR/EULAR TIS. It is a set of 8 designated muscles tested unilaterally (generally on right side) -

which include 1 axial, 5 proximal (2 upper extremity, 3 lower extremity), and 2 distal muscles (1 upper, 1 lower extremity). Total score for unilateral testing ranges from 0 to 80, and bilateral testing ranges from 0 to 150 with normal strength represented by a higher score at or near the top of the scale.

Myositis Disease Activity Assessment Tool (MDAAT)

MDAAT is a combined tool that captures the physician's assessment of disease activity of various organ systems - constitutional, cutaneous, pulmonary, gastrointestinal, joints and cardiovascular, muscular using:

- Myositis Intention to Treat Activity Index (MITAX), a scale from 0 ("Not present in the last 4 weeks") to 4 ("New - in the last 4 weeks [compared to the previous 4 weeks]")

AND

- Myositis Disease Activity Assessment Visual Analogue Scales (MYOACT), a 10 cm VAS assessing disease activity in the last 4 weeks of various organ systems from 0 cm ("No evidence of disease activity") to 10 cm ("Extremely active or severe disease activity"), disease activity being defined as potentially reversible pathology or physiology resulting from the myositis. Left end of line = no evidence of disease activity, midpoint of line = moderate disease activity, and right end of line = extreme or maximum disease activity.

If any particular organ domain is inactive (using VAS) or all events under an organ domain is scored as 0 (using MITAX) at baseline, post randomization the organ domain can remain as inactive or scored 0 provided there are no new activity or new event observed.

Patient Experience In-trial Qualitative Interviews

Patient experience in-trial qualitative interviews will be performed as part of the clinical trial, to document the experience of treatment and trial participation from the patient perspective. Specifically, the interviews are expected to capture 1) the patient experience of treatment and participation in the clinical study, 2) the patient experience of changes (or no change) in symptoms and the ability to function or perform activities that are important to the patient, and 3) the patient perspective on the meaningfulness and importance of study endpoints, including score change in PRO assessments. The interviews will follow a one-on-one format and will be conducted via remotely, based on an interview guide. Each interview will be approximately 60 minutes and will be completed within 2 weeks of the participant's completion of the End of Treatment or Early Termination visit for the DBPC period of the study.

The interviews will be offered to all participants from selected study sites. Participants from the selected sites will be provided with a description of the qualitative interview. Details about the qualitative interviews will be included in the clinical trial informed consent form and ethics and IRB review submissions.

All interviews will be conducted by trained moderators and will be audio recorded. The content of the interview will be transcribed, and the audio recording will be destroyed to protect participant

privacy. All personal information will be removed from the transcripts. Using the interview transcripts, dominant trends will be identified in each interview and then compared across the results of the other interviews to generate themes or patterns in the way participants describe their treatment and clinical trial experiences as well as their perceptions of treatment benefit and elements such as meaningful change in PRO measure scores over the trial period.

Should an interviewer become aware of any potential adverse event during the remote interview, the interviewer will share the relevant information with the participant's clinical site staff within 24 hours. The clinical site will be responsible for follow-up with the participants and the site's principal Investigator will be responsible for determining the clinical significance of the event.

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Appendix 11 Protocol Amendment History

The information for the current amendment is on the title page.

Protocol Version 4.0 (02 August 2023)

Overall Rationale for the Amendment

The rationale for this protocol amendment is to align with standard of care and enable participation of patients impacted by this change.

Section # and Name	Description of Change	Brief Rationale
CCI [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED]
[REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]
2.3. Benefit/Risk Assessment	Added new clinical information of enpatoran.	To update clinical knowledge of enpatoran.
2.3.1. Risk Assessment	Updated the summary of data and mitigation strategies for clinically significant cardiac arrhythmia.	To align with most current information and to align risk assessment table throughout the enpatoran clinical development program.
2.3.1. Risk Assessment 8.3.8 Management of Adverse Events	Added QTc change from baseline of ≥ 60 ms as a clinical sign to be managed.	To improve the risk mitigation strategy.
2.3.5 Overall Benefit: Risk Conclusion	Reworded overall benefit-risk conclusion.	To improve clarity.
CCI [REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED]
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[REDACTED]	[REDACTED]	[REDACTED] [REDACTED]
[REDACTED]	[REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]
5.2 Exclusion Criteria	Defined QTc values to be considered clinically significant abnormality.	Omission in earlier versions.
5.2 Exclusion Criteria Appendix 6	Decrease washout period for Ig from 12 to 8 weeks prior to Day 1 for patients who have received ≤ 2 doses	To facilitate participation of patients who do not respond to or have infusion/injection related reaction to Ig.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria Appendix 6	Decreased wash-out period for JAK-STAT pathway inhibitors from ≤ 8 to ≤ 4 weeks prior Day 1.	Correction as previous washout period was unnecessarily long.
5.2 Exclusion Criteria 6.8.3 Prohibited Medicines Appendix 6	Added use of treatments approved only in non-IIM indications as prohibited.	Omission in earlier versions.
8.2.4 Clinical Safety Laboratory Assessments Appendix 5	Added alkaline phosphatase isoenzyme testing to list of local laboratory tests.	Omission in earlier versions.
9.3 Analyses Sets	Updated the description of subgroups for analyses.	Previous omission (some patients with PM may also have rash) and alignment with updated eligibility criteria.
Appendix 6	Added more examples of investigational agents, all of which are prohibited.	To reduce incompliance by improving clarity.
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Throughout	Minor editorial and document formatting revisions.	Administrative and editorial updates.

ASyS = anti-synthetase syndrome, BMI = body mass index, CDASI = Cutaneous Dermatomyositis Area and Severity Index, DM = dermatomyositis, eGFR = estimated glomerular filtration rate, Ig = immunoglobulin, IIM = idiopathic inflammatory myopathies, JAK-STAT = Janus kinase/signal transducers and activators of transcription, MMT = manual muscle testing, MSA = myositis specific autoantibodies, PM = polymyositis.

Protocol Version 3.0 (03 April 2023)

Overall Rationale for the Amendment

The rationale for this protocol amendment is the following:

Establishment of an Independent Data Monitoring Committee (IDMC) for a close monitoring of the potential safety risks of enpatoran.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 – Synopsis Section 6.3.2 – Blinding Method Section 9.4.4 – Sequence of Analyses Appendix 2 – Study Governance	Replaced the SMC by an IDMC to review study information during the conduct of the study in an unblinded manner. Added information on data review by IDMC and Firewall Team.	To have a closer monitoring for potential safety risks of enpatoran.

Protocol Version 2.0 (20 March 2023)

Overall Rationale for the Amendment

The rationale for this protocol amendment is the following:

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considerations, and to update the protocol in alignment with the Investigator Brochure (IB) Versions 6.0 and 7.0.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 2.1 Study Rationale Section 2.3.1 Risk Assessment Section 4.3 Justification for Dose	Updated information based on completed Study MS200569_0040.	To align with IB v7.0.
Section 1.1 Synopsis Section 4.1 Overall design	Added clarification that for certain countries, OLE may only be implemented after approval by local Authorities.	To comply with country-specific requirements.
Section 1.3.1 Double-Blind Placebo Controlled Treatment Period	Added ECG at Week 4	To have a closer monitoring for potential risk of arrhythmias.
Section 2.3.1 Risk Assessment	Added participant's education by site to identify early symptoms and on over-the-counter medicinal products/diet supplements with CCI [REDACTED], as mitigation strategies for the risk of CCI [REDACTED].	To reduce participants' risk of experiencing CCI [REDACTED]
CCI [REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED]
CCI [REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED]
Section 6.8.2 Permitted Medicines	Added guidance on intestinal breast cancer resistance protein (BCRP) inhibition drug-drug interaction potential.	To align with IB v6.0 and v7.0
Section 8.2.4 Clinical Safety Laboratory Assessments Appendix 5	Updated information that evaluation of autoantibody status (if historical data are not available) is to be done locally.	To complete the information as this assessment is to be done locally.
Section 8.3.8 Management of Adverse Events (Including AESI)	Added QTc prolongation on ECG of ≥ 500 ms as clinical sign to be managed.	CCI [REDACTED] [REDACTED]
Section 9.2 Sample Size Determination	Added details on methodology for calculation of sample size.	To complete information.
Section 9.4.1 Efficacy Analyses	Added information on imputation of missing values.	To complete information.
Section 9.4.4 Sequence of Analyses	Added information on interim analysis	To complete information.
Appendix 2 Study Governance	Added information on approximated number of participating sites and countries.	To complete information.
Appendix 2 Study Governance	Added information on the sharing of study results, removal of reference to EudraCT.	To correct an error and complete information.
Throughout	Minor editorial and document formatting revisions.	Administrative and editorial updates.

Appendix 12 Sponsor Signature Page

Study Title: A Phase IIa, Randomized, Parallel, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Enpatoran in Dermatomyositis and Polymyositis Participants receiving Standard of Care

Regulatory Agency Identifying Numbers: CCI
EUCT number: 2022-501351-82-00
ClinicalTrials.gov identifier: NCT05650567

Clinical Study Protocol Version: 24 June 2024/Version 5.0

I approve the design of the clinical study:

PPD

Signature

Date of Signature

Name, academic Degree:

Function/Title:

Institution:

Address:

General Merck Phone Number:

General Merck Fax Number:

PPD

Merck Healthcare KGaA

Frankfurter Str. 250, Darmstadt, Germany

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Not Applicable

Appendix 13 Coordinating Investigator Signature Page

Study Title: A Phase IIa, Randomized, Parallel, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Enpatoran in Dermatomyositis and Polymyositis Participants receiving Standard of Care

Regulatory Agency Identifying Numbers:

CCI

EUCT number: 2022-501351-82-00

ClinicalTrials.gov identifier: NCT05650567

Clinical Study Protocol Version: 24 June 2024/Version 5.0

Site Number:

I approve the design of the clinical study, am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, ICH GCP (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signature

Date of Signature

Name, academic degree:

Function/Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

PPD

Appendix 14 Principal Investigator Signature Page

Study Title: A Phase IIa, Randomized, Parallel, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Enpatoran in Dermatomyositis and Polymyositis Participants receiving Standard of Care

Regulatory Agency Identifying Numbers: CCI
EUCT number: 2022-501351-82-00
ClinicalTrials.gov identifier: NCT05650567

Clinical Study Protocol Version: 24 June 2024/Version 5.0

Site Number:

I am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, ICH GCP (Topic E6) and all applicable Health Authority requirements and national laws.

I also understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for complying with the regulatory requirements. Therefore, I agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

Signature

Date of Signature

Name, academic degree:

Function/Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address: