

Integrated Analysis Plan

Study Number:	MS200569_0041	
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Integrated Analysis Plan Author:	Coordinating Author	
	Biostatistician, Merck	PPD
	Function	Author(s) / Data Analyst(s)
	PPD	
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Integrated Analysis Plan Reviewers:	Function	Name
	Statistical Programmer, Merck	PPD
	Statistical Programmer, Merck	
	Medical Director, Merck	
	Global Patient Safety Strategy Lead, Merck	
	Clinical Lead, Merck	
	PRO Specialist, Merck	
	Data Management Lead, Merck	
	Clinical Pharmacology Lead, Merck	
	Clinical PK, Merck	
	Biomarker Lead, Merck	
	Medical Writer Lead, Merck	
	Global Regulatory Lead, Merck	

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Approval Page

Integrated Analysis Plan: MS200569_0041

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

Approval of the IAP by all Merck Data Analysis Responsible has to be documented within EDMS via eSignature. With the approval, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

By using eSignature, the signature will appear at the end of the document.

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2 List of Abbreviations and Definition of Terms

CCI	
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	aspartate Aminotransferase
ACR	American College of Rheumatology
ATC	Anatomical Therapeutic Chemical Classification
BID	Bis In Die (twice daily)
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
CDASI	Cutaneous Dermatomyositis Area and Severity Index
CDASI-A	Cutaneous Dermatomyositis Area and Severity Index - Activity
CDASI-D	Cutaneous Dermatomyositis Area and Severity Index - Damage
CDISC	Clinical Data Interchange Standards Consortium
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CS	Corticosteroid
CSM	Core Set Measures
(e)CRF	(electronic) Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
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DBPC	Double-Blind, Placebo-Controlled
DLCO	Diffusing capacity of the lungs for carbon monoxide
DM	Dermatomyositis
DOI	Definition of Improvement
ECG	Electrocardiogram
EDMS	Electronic Document Management System

EEA	European Economic Area
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HHD	Hand-held dynamometry
HTA	Health Technology Assessment
HRQOL	Health Related Quality of Life
IAP	Integrated Analysis Plan
ICE	Intercurrent Event
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
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IMACS	International Myositis Assessment and Clinical Studies
IWRS	Interactive Web Response System
LCI	Lower Confidence Interval
LLOQ	Lower Limit of Quantification
LOCF	Last Observation Carried Forward
MCS	Mental Component Summary
MDAAT	Myositis Disease Activity Assessment Tool
MMT	Manual Muscle Testing
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCA	Non-Compartmental Analysis
ND	Not Determined
ne	Not Evaluable
N, n	N = number of subjects included in the analysis set ; n = number of non-missing values

N.R.	No Result or result not valid
OLE	Open Label Extension
PCS	Physical Component Summary
PD	Pharmacodynamics
PGA	Physician Global Activity
PK	Pharmacokinetics
PKAS	Pharmacokinetic Analysis Set at DBPC Period
PKAS-OLE	Pharmacokinetic Analysis Set at OLE Period
PM	Polymyositis
PRO	Patient-Reported Outcomes
PT	Preferred Term
PtGA	Patient Global Activity
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SCR	Screening Analysis Set
SD	Stable Disease or Standard Deviation
SDTM	Study Data Tabulation Model
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SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TIS	Total Improvement Score
UCI	Upper Confidence Interval
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	7 November 2023	PPD	Not applicable
2.0	14 March 2025	PPD	Replaced CCI [REDACTED] Section 6.2: replaced the trigger for the interim analysis from 20 participants with 24-week follow-up to 18 participants randomized. Section 6.3: removed the statement of only data up to DBPC W24 to be analyzed. Section 7: added IA trigger update. Section 9.2: specified that time of assessment will not be considered when deriving baseline value for routine urinalysis parameters. Section 11.3: updated categorization for the daily prednisone-equivalent CS dose at Baseline. Section 15: removed the statement that only adverse events which started during the DBPC period will be considered for the primary analysis. Section 16.2: added derivation for NF-kB gene signature.
3.0	10 July 2025	PPD	Added section 6.5 Analysis after Early Termination of the Study. Section 9.7: Updated time window.

4 Purpose of the Integrated Analysis Plan

The purpose of this IAP is to document technical and detailed specifications for the primary analysis of data collected for protocol MS200569_0041. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

Additional analyses not covered by this IAP such as, for instance, CCI [REDACTED] CCI [REDACTED] analyses not pre-defined in the protocol or additional sub-group analyses planned for HTA submission will be listed in the respective Data Analysis Responsibility form which is stored in the Electronic Document Management System (EDMS) together with this IAP.

The IAP is based upon Section 9 (Statistical Considerations) of the study protocol and protocol amendments (if applicable) and is prepared in compliance with ICH E9. It describes analyses planned in the protocol, except integrated Population PK, PK/PD and/or exposure-response modeling activities, CCI [REDACTED] analyses, and analyses of serum CCI [REDACTED] which will be reported separately. Details of the 2 independent data monitoring committee (IDMC) analyses for

review of the participants' safety without formal statistical analysis and the interim analysis are also provided in appendices.

The wording used in this IAP is chosen to best match the respective wording in the study protocol template, the CSR template, Clinical Data Interchange Standards Consortium (CDISC) requirements and special requirements for table layouts. Therefore, the following approach is used:

- Generally, the term 'participant' will be used instead of 'subject' or 'patient'. However, in tables and listings the term 'subject' will be used to match CDISC requirements, except for in-text tables where 'participant' will be used to match the CSR and protocol templates.
- Similarly, the term 'study intervention' will be used in this document instead of 'treatment' to match protocol and CSR templates, however, tables and listings will use 'treatment' for brevity reasons. Exceptions from this rule are commonly used terms like "on-treatment", "treatment-emergent", "treatment policy", "subject-years", "by-subject", or names of eCRF pages like "Treatment Termination" page.

5 Objectives and Estimands

Objectives	Estimand attributes	IAP Section	Analysis*
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	<u>Endpoint:</u> 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 Core Set Measures: - Physician Global VAS derived from MDAAT - Patient Global VAS - MMT-8 - HAQ-DI - Most abnormal muscle-associated enzymes - Extramuscular Activity Assessment derived from MDAAT <u>Population:</u> DM and PM patients <u>Treatment:</u> Enpatoran compared to placebo CCI [REDACTED] ■ [REDACTED] ■ [REDACTED] ■ [REDACTED] ■ [REDACTED] ■ [REDACTED] ■ [REDACTED] ■ [REDACTED] ■ [REDACTED] <u>Population-Level Summary:</u> difference of means and 95% confidence intervals	14.1	Primary

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Population-Level Summary: Difference of means and 95% CI

Objectives	Estimand attributes	IAP Section	Analysis*
	<u>Endpoint:</u> 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) <u>Population:</u> DM and PM patients <u>Treatment:</u> Enpatoran compared to placebo CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] <u>Population-Level Summary:</u> Number and percentage of responders; difference to placebo with 95%CI	14.2.3	Primary

Objectives	Estimand attributes	IAP Section	Analysis*
To evaluate the efficacy on cutaneous disease activity of DM (in DM participants and PM participants with rash, defined as CDASI-A $\geq$ 7) with enpatoran compared to placebo during the DBPC period	<u>Endpoint:</u> - 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 IGA skin activity at each visit from Week 4, up to Week 24 <u>Population:</u> DM and PM patients with rash <u>Treatment:</u> Enpatoran compared to placebo CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] <u>Population-Level Summary:</u> difference of means and confidence intervals	14.2.4	Primary
To evaluate the safety and tolerability of enpatoran in DM and PM participants during the CCI [REDACTED] (according to treatment received during DBPC)	<u>Endpoints:</u> - Occurrence of TEAEs, SAEs and AESI during OLE period - Changes in laboratory parameters - Change in vital signs - Change in 12-lead ECG <u>Population:</u> DM and PM patients <u>Treatment:</u> Enpatoran compared to placebo CCI [REDACTED] <u>Population-Level Summary:</u> Descriptive statistics	15	Secondary

Objectives	Estimand attributes	IAP Section	Analysis*
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*The primary analysis will be conducted after the DBPC part of the study is completed, and the secondary analysis will be conducted after the OLE part is completed.

6 Overview of Planned Analyses

6.1 Analyses for IDMC Meetings

An IDMC will be responsible for the safety evaluation and will make recommendations for the study. CCI

In total 2 IDMC meetings are planned.

- The first IDMC meeting will take place after at least 8 participants have had a minimum of 12 weeks of treatment with a minimum of 4 participants per subtype (4 DM and 4 PM) having received the 12 weeks of treatment (depending on the recruitment, an early data cut-off may be considered for review).

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- The second IDMC meeting is planned after at least 16 participants have had a minimum of 16 weeks of treatment with a minimum of 6 participants per subtype (6 DM or 6 PM) having received the 16 weeks of treatment (depending on the recruitment, an early data cut-off may be considered for review).

Once a trigger is met, a data snapshot will be taken for provision of IDMC outputs. There will be no data cut-off applied.

During the study, the meeting schedule may be revised by the IDMC after reaching consensus by the core members. Details of analyses for IDMC meetings are specified in [appendix 18.1](#).

6.2 Interim Analyses

An interim analysis may be conducted. An IDMC and an internal Firewall team will be responsible for the review of efficacy and safety data, and the assessment of benefit-risk.

The interim analysis will occur after 18 participants are randomized.

Details on the conduct of the interim analysis can be found in the External Data Monitoring Committee Charter and the Firewall Team Charter.

Details of analyses for the interim analysis are specified in [appendix 18.1](#).

6.3 Primary Analysis after the DBPC period

The study will be double-blind during the 24-week DBPC period. Study team will be blinded until the DBPC period is completed at which time full analysis will be performed (DBPC analysis, Week 24). Participants and site personnel will remain blinded until the end of the study.

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 prematurely during DBPC, the protocol deviations are determined, and the database is locked for the primary analysis.

The analyses for primary analysis are specified in the different sections of the IAP and in the table of objectives and estimands from [section 5](#).

6.4 Secondary Analysis after the OLE period

A secondary 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]).

The optional OLE treatment Period will provide data on long-term exposure and allow all completers of the DBPC period 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.

All data collected during the DBPC and the OLE periods will be part of the analysis and will be considered in the output, except in figures for change from baseline, shift tables compared to baseline, and AE tables by Preferred and System Organ Class in which the OLE Period only will be considered.

6.5 Analysis After Early Termination of the Study

Further to the review of the interim analysis results, it was concluded that there is a very low probability that enpatoran would demonstrate clinically meaningful benefit for participants if the study were to continue as planned. The study will therefore be prematurely terminated.

Consequently, the scope of analyses has been reduced. The primary and secondary analyses outlined respectively in [Section 6.3](#) and [Section 6.4](#) will not be performed as planned. However, a single analysis using all data available at final database lock will be performed for an abbreviated CSR.

The analyses considered relevant for this purpose are listed below:

- Participant disposition
- Important protocol deviations
- Enrollment details
- Demographics, medical history, and disease diagnosis
- Previous and concomitant medications/corticosteroids
- Treatment compliance and exposure
- Efficacy analyses:
 - Total Improvement Score
 - International Myositis Assessment and Clinical Studies (IMACS) Response
 - All individual components of the Total Improvement Score
 - Cutaneous Dermatomyositis Area and Severity Index-A (CDASI-A) and Cutaneous Dermatomyositis Area and Severity Index-D (CDASI-D)
 - Investigator Global Assessment of skin
- Safety analyses:
 - Overview of treatment-emergent adverse events (TEAEs)
 - Overview of TEAEs leading to treatment discontinuation
 - TEAEs by SOC and PT (all, treatment-related, serious, non-serious, treatment related serious, leading to temporary treatment discontinuation, leading to permanent treatment discontinuation, by worst grade)
 - TEAEs of special interest
 - Listings of deaths, AEs, SAEs
 - Laboratory assessments (hematology, biochemistry, urinalysis)
 - Vital signs
 - ECG results
- CCI analysis: CCI

The analyses will be conducted as planned in this IAP. The list of all outputs planned for this analysis is reported in a separate document (see [Section 18.1](#)).

7 Changes to the Planned Analyses in the Clinical Study Protocol

- Addition compared to the protocol: Definition of Full Analysis Set with rash at start of DBPC (FAS_rash), definition of Full Analysis Set at OLE period with rash at start of DBPC (FAS_rash-OLE), definition of Pharmacodynamic Analysis Set at OLE period (PD-OLE)), and definition of Pharmacokinetic Analysis Set at OLE period (PKAS-OLE) have been specified in the IAP.
- Change from the protocol: Definition of the Safety Analysis Set at OLE period (SAF-OLE) is modified compared to the protocol.
Original definition: 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.
Updated definition: All participants, who were administered any dose of study intervention in the OLE period. Analyses will consider participants as treated in the DBPC period. This analysis set will be used for safety in the OLE period.
- Change from the protocol: Definition of the Pharmacokinetic Analysis Set (PK) is modified compared to the protocol.
Original definition: 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.
Updated definition: All participants, who receive at least 1 dose of active study intervention (i.e. enpatoran), have no important protocol deviations or events affecting PK, and provide at least 1 measurable postdose concentration. A measurement below the lower limit of quantification (BLQ) is considered a valid measurement. Participants will be analyzed per the actual study intervention they received. This analysis set will be used for PK analyses in the DBPC period.
- Change from the protocol: Definition of the Pharmacodynamic Analysis Set (PD) is modified compared to the protocol.
Original definition: 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.
Updated definition: All participants, who receive at least one dose of study intervention, have no important protocol deviations or events affecting PD, and provide at least one measurable PD endpoint postdose.
- Change from the protocol: Definition of the method on which the confidence intervals of total improvement scores will be based.
Original definition: 95% CIs will be based on parametric (t-test) or non-parametric test.
Updated definition: 95% CIs will be based on parametric (t-test).

8 Analysis Sets and Subgroups

8.1 Definition of Analysis Sets

Each analysis set will be described for each treatment group (enpatoran, placebo) separately, unless specified otherwise.

Screening Analysis Set (SCR)

All participants, who provided informed consent, regardless of the participant's randomization and study intervention status in the study.

Full Analysis Set (FAS)

All randomized participants. A 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.

Full Analysis Set with rash at start of DBPC, defined as CDASI-A ≥ 7 (FAS_rash)

All randomized participants with a rash defined as a value for CDASI-A ≥ 7 at baseline at start of the DBPC period. A 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.

Safety Analysis Set (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.

Pharmacokinetic Analysis Set (PK)

All participants, who receive at least 1 dose of active study intervention (i.e. enpatoran), have no important protocol deviations or events affecting PK, and provide at least 1 measurable postdose concentration. A measurement below the lower limit of quantification (BLQ) is considered a valid measurement. Participants will be analyzed per the actual study intervention they received. This analysis set will be used for PK analyses in the DBPC period.

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[REDACTED]

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Full Analysis Set at OLE period (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.

Full Analysis Set at OLE period with rash at start of DBPC, defined as CDASI-A ≥ 7 (FAS_rash-OLE)

All participants, who were administered any dose of study intervention in the OLE period and with a rash defined as a value for CDASI-A ≥ 7 at baseline at start of DBPC. Analyses will consider participants as randomized in the DBPC period. This analysis set will be used for efficacy analyses in the OLE period.

Safety Analysis Set at 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 DBPC period. This analysis set will be used for safety in the OLE period.

Pharmacokinetic Analysis Set at OLE period (PKAS-OLE)

All participants, who receive at least 1 dose of active study intervention (i.e. enpatoran) in the OLE period, have no important protocol deviations or events affecting PK during the DBPC or the OLE period, and provide at least 1 measurable postdose concentration. A measurement below the lower limit of quantification (BLQ) is considered a valid measurement. Participants will be analyzed per the actual study intervention they received. This analysis set will be used for PK analyses in the OLE period.

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Analyses per Analysis Set

The following table summarizes the use of the analysis sets in the different analyses.

	Analysis Set for primary analysis (DBPC analysis)						Analysis Set for secondary analysis (OLE analysis)				
Analyses	FAS	FAS_rash	SAF	PK	PD	PD2	FAS-OLE	FAS_rash-OLE	SAF-OLE	PK-OLE	PD-OLE
Demographics and Other Baseline Characteristics	✓						✓				
Previous and Concomitant Therapies	✓						✓				
Study Intervention: Compliance and Exposure			✓						✓		
Efficacy Analyses	✓						✓				
CDASI-A, CDASI-D and IGA skin activity during the DBPC period		✓						✓			
Safety Analyses			✓						✓		
Pharmacokinetics				✓						✓	

8.2 Subgroup Definition and Parameterization

The following subgroups of the FAS/SAF will be considered for primary and secondary efficacy and safety endpoints (assuming there is at least 40% representation per group), in the primary analysis after the DBPC period:

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

Patients with rash at baseline will be defined as a value for CDASI-A at baseline ≥ 7 at start of DBPC period.

All subgroup analyses will be exploratory, no adjustment for multiplicity will be performed.

9 General Specifications for Data Analyses

Unless otherwise specified, data will be summarized for each study group separately. Study intervention groups will be labeled “Placebo”, “Enpatoran 100 mg BID” in the primary analysis after the DBPC period; they will be labeled “Placebo / Enpatoran 100 mg BID” and “Enpatoran 100 mg BID / Enpatoran 100 mg BID” in the secondary analysis after the OLE period.

Unless otherwise specified, continuous variables will be summarized using descriptive statistics, i.e., the number of participants with non-missing values (n), number of participants with missing

values (nmiss) calculated as $N - n$, mean, standard deviation (SD), median, 25th percentile (Q1) and 75th percentile (Q3), minimum, and maximum. In case descriptive statistics cannot be calculated because there no sufficient subjects (for instance, confidence interval), Not Determined (ND) will be specified in the output.

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise stated the calculation of proportions will be based on the number of participants of the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

Unless otherwise specified, descriptive statistics by nominal visit or time point, e.g., for laboratory measurements, will include data from both scheduled and unscheduled visits after applying visit/time windowing ([section 9.7](#)). Unscheduled visits will also be included in the derivation of baseline or worst post-baseline values.

If confidence intervals (CIs) are to be calculated, these will be two-sided with a confidence probability of 95%, unless otherwise specified in this IAP.

In order to provide overall estimates of study intervention effects, data will be pooled across sites. The “site” factor will not be considered in statistical models due to the high number of participating sites in contrast to the anticipated small number of participants randomized at each site.

All statistical analyses described in this IAP will be performed using SAS® software version 9.4 or higher. Phoenix® WinNonlin® version 8.3 or higher (Certara, L.P., Princeton, New Jersey, USA) will also be used to derive PK parameters.

9.1 Data handling after Cut-off Date

By its nature, data after cut-off may be incomplete and subject to further change and will not be used for summary statistics, statistical analyses, listings or imputations.

Stop dates are not affected by this rule, e.g. a stop date of AEs, which starts prior to the cut-off, but stops after date of cut-off, will not be changed.

9.2 Definition of Baseline and Change from Baseline

Baseline at start of DBPC is defined as the last non-missing measurement prior to the first administration of study intervention received during the DBPC period. In case a participant was randomized but did not receive the study intervention, the last non-missing measurement prior to the date of randomization will be used as baseline value. For all the efficacy endpoints of [Section 14](#), an assessment collected the same day as the first administration of study intervention received during the DBPC period will be considered in the derivation of the Baseline at start of DBPC, whatever the timing of the evaluations and study interventions.

Baseline at start of OLE is defined as the last non-missing measurement prior to the first administration of study intervention received during the OLE period. Baseline at start of OLE will be used in the outputs for the secondary analysis (OLE analysis), except in tables for summary

statistics and listings where both baseline values and definitions will be considered, unless otherwise specified. For all the efficacy endpoints of [Section 14](#), an assessment collected the same day as the first administration of study intervention received during the OLE period will be considered in the derivation of the Baseline at start of OLE, whatever the timing of the evaluations and study interventions.

For other endpoints, if an assessment which is planned to be performed before randomization or study intervention per protocol is performed on the same day as the randomization or start of study intervention, respectively, but the assessment time is not available, it will be assumed that it was performed prior and will be considered for derivation of baseline.

Routine urinalysis can be performed pre- or post-dose as per protocol. Time of assessment will therefore not be considered when deriving the baseline value.

Absolute and percent changes from Baseline are defined as

- absolute change = visit value – baseline value
- percent change = $100 * (\text{visit value} - \text{baseline value}) / \text{baseline value}$

9.3 Study Day / Study Intervention Day

DBPC Day 1 is the day of first dose of study intervention during DBPC part, the day before is Day -1 (no Day 0 is defined).

OLE Day 1 is the day of first dose of study intervention during OLE part.

Study day / Study intervention day is defined relative to DBPC Day 1.

9.4 Definition of Duration and ‘Time Since’ Variables

Durations in days will be calculated by the difference of start and stop date + 1 (e.g., AE duration [days] = stop date – start date + 1) if not otherwise specified.

The time since an event (e.g., time since documented diagnosis) will be calculated as (reference date - date of event).

9.5 Conversion Factors

The following conversion factors will be used:

- 1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days
- 1 kg = 2.20462 lbs
- 1 cm = 0.39370 in
- From °F to °C: $(^{\circ}\text{F} - 32) / 1.8000$

9.6 Date of Last Contact

The date of last contact will be derived for all participants using the latest complete date prior to or at the data cut-off date among the following:

- AE start and end dates
- Date of last study intervention
- Date for any study assessments
- Date of study termination
- Date of death

Only dates associated with actual examinations of the participant reported in the eCRF will be used in the derivation. Dates associated with a technical operation unrelated to participant status such as the date a blood sample was processed will not be used.

9.7 Time Window

Unless otherwise specified, study measurements (including those at early termination) will be assigned an analysis visit based on their actual assessment date as described in the tables below.

- DBPC period
 - For data collected at each visit of the DBPC period:

Analysis Visit	Target Day	eCRF Visit	Window Range
DBPC Day 1	1	Any	1
DBPC Week 4 Day 29	29	Any	> 1 – 42
DBPC Week 8 Day 57	57	Any	43 – 70
DBPC Week 12 Day 85	85	Any	71 – 98
DBPC Week 16 Day 113	113	Any	99 – 126
DBPC Week 20 Day 141	141	Any	127 – 154
DBPC Week 24 Day 169	169	Any	155 – 176
		Any apart from Safety Follow-up visit	177 – 182
DBPC Safety Follow-up Visit Week 26 Day 183	183	Safety Follow-up visit	177 – 182
		Any	> 182

- For data collected at DBPC Day 1, DBPC Week 8, DBPC Week 16, DBPC Week 24, DBPC Safety Follow-up Visit Week 26:

Analysis Visit	Target Day	eCRF Visit	Window Range
DBPC Day 1	1	Any	1
DBPC Week 8 Day 57	57	Any	> 1 – 84
DBPC Week 16 Day 113	113	Any	85 – 140
DBPC Week 24 Day 169	169	Any	141 – 176
		Any apart from Safety Follow-up visit	177 – 182
DBPC Safety Follow-up Visit Week 26 Day 183	183	Safety Follow-up visit	177 – 182
		Any	> 182

- For data collected at DBPC Day 1, DBPC Week 12, DBPC Week 24:

Analysis Visit	Target Day	Window Range
DBPC Day 1	1	1
DBPC Week 12 Day 85	85	> 1 – 126
DBPC Week 24 Day 169	169	≥ 127

- OLE period

- For data collected at OLE Day 1, OLE Week 4, OLE Week 8, OLE Week 12, OLE Week 24:

Analysis Visit	Target Day	Window Range
OLE Day 1 ¹	1	1
OLE Week 4 Day 29	29	> 1 – 42
OLE Week 8 Day 57	57	43 – 70
OLE Week 12 Day 85	85	71 – 126
OLE Week 24 Day 169	169	127 – 175

- For data collected at OLE Day 1, OLE Week 12, OLE Week 24:

Analysis Visit	Target Day	Window Range
OLE Day 1 ¹	1	1
OLE Week 12 Day 85	85	> 1 – 126
OLE Week 24 Day 169	169	≥ 127

- For data collected at OLE Day 1, OLE Week 4, OLE Week 12, OLE Week 24, OLE Safety Follow-up Visit Week 26:

Analysis Visit	Target Day	eCRF Visit	Window Range
OLE Day 1 ¹	1	Any	1
OLE Week 4 Day 29	29	Any	> 1 – 56
OLE Week 12 Day 85	85	Any	57 – 126
OLE Week 24 Day 169	169	Any	127 – 176
		Any apart from OLE Safety Follow-up visit	177 – 182
OLE Safety Follow-up Visit Week 26 Day 183	183	OLE Safety Follow-up visit	177 – 182
		Any	> 182

- For data collected at OLE Day 1, OLE Week 12, OLE Week 24, OLE Safety Follow-up Visit Week 26:

Analysis Visit	Target Day	eCRF Visit	Window Range
OLE Day 1 ¹	1	Any	1
OLE Week 12 Day 85	85	Any	> 1 – 126
OLE Week 24 Day 169	169	Any	127 – 176
		Any apart from OLE Safety Follow-up visit	177 – 182
OLE Safety Follow-up Visit Week 26 Day 183	183	OLE Safety Follow-up visit	177 – 182
		Any	> 182

¹ 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).

In case multiple assessments are assigned to the same window, the closest value to the target day will be considered for analysis. If two values are observed with the same distance to the target day (one before and one after), then the earlier value will be used for analysis.

In case several time points are scheduled on a same day, specifications will be provided for the related parameters.

9.8 Definition of On-treatment Period

The on-treatment period for the primary analysis (DBPC analysis) is defined as: the time from the first dose of study intervention received during the DBPC period, to the date of last contact during the DBPC period (including safety follow-up).

The on-treatment period for the secondary analysis (OLE analysis) is defined as: the time from the first dose of study intervention received during the DBPC period, to the date of last contact during the OLE period (including safety follow-up).

9.9 Exposure time

Duration of exposure to study intervention = end date – date of first dose of study intervention +1, where:

- end date is the date of last dose of study intervention.

9.10 Imputation of Missing Data

Disease history:

Incomplete dates for documented diagnosis of DM or PM will be imputed as follows:

- If the day is missing, it will be imputed to the 1st day of the month.
- If both day and month are missing and the year is available, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

Exposure:

In case the start date of study intervention is missing, it is assumed that the first dose of study intervention is given at the randomization date. The randomization date will replace incomplete dates of the first dose of study intervention.

Adverse events (AEs):

Incomplete AE-related dates will be imputed as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year, are equal to the start of study intervention then the onset date will be imputed by the minimum of start of study intervention and AE resolution date (if not missing).
- In all other cases, the missing onset day or missing onset month will be imputed by 1.
- Incomplete stop dates will be imputed by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case, the date of death will be used to impute the incomplete stop date.
- In all other cases, the incomplete stop date will not be imputed.

Previous and concomitant medication:

Incomplete previous/concomitant medication start and stop dates will be imputed as presented in [Table 1](#).

For the derivation of previous and concomitant medications, the following rules will be applied:

Previous Medication:

- Start date $\leq$ Start of study intervention OR
- Start date = Missing

Concomitant Medication:

- End date $\geq$ Start of study intervention AND (Start date $\leq$ End of study intervention OR Start date=Missing) OR
- End date = Missing AND (Start date $\leq$ End of study intervention OR Start date = Missing)

Table 1 Imputation rules for missing/incomplete start/end dates of medication

	Start Date	End Date
Day missing only	Day = 1	Day = Last day of month
Month missing	Day = 1 Month = Jan	Day = 31 Month = Dec
Year missing	Date = Missing No imputation	
All	if imputed date > date of death: imputation by date of death	

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9.11 Scoring and Handling of Missing Item-level Data for Clinician-Reported Outcomes

9.11.1 Total Improvement Score (TIS)

The American College of Rheumatology/European League Against Rheumatism Total Improvement Score (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 Group.

In this study, the 6 CSM are:

1) Global Disease Activity/Physician Global Activity (PGA)

Specifications for PGA are provided in [section 9.11.2.1](#).

2) Patient Global Activity (PtGA)

Specifications for PtGA are provided in [section 9.12.1](#).

3) Manual Muscle Testing (MMT)-8 Score

Specifications for MMT are provided in [section 9.11.3](#).

4) Health Assessment Questionnaire-Disability Index (HAQ-DI)

Specifications for HAQ-DI are provided in [section 9.12.2](#).

5) Most abnormal muscle-associated enzymes

For each participant, the most abnormal enzyme is the enzyme at baseline at start of DBPC (as defined in [Section 9.2](#)) with the highest ratio (absolute value / upper limit of normal range) among: Creatinine Kinase, Lactate Dehydrogenase, Aspartate Aminotransferase, Alanine Aminotransferase and Aldolase.

6) Extramuscular activity

Specifications for Extramuscular activity are provided in [section 9.11.2.2](#).

To calculate the TIS, the absolute percent change ($[\text{final value} - \text{baseline value}] / \text{range}$) x 100 is first calculated for each of the 6 core measures described above. For primary analysis and secondary analysis, baseline at start of DBPC will be considered in the derivation. Based on the absolute percent change for each core measure, an improvement score will be assigned as shown in the table below. These individual improvement scores will then be summed to calculate the TIS. A TIS corresponds to the degree of improvement with higher scores indicating greater improvement. The TIS scale ranges from 0 to 100 with thresholds for minimal (≥ 20), moderate (≥ 40) and major (≥ 60) improvement in the combined 6 CSM.

Core Set Measure	Data source	Direction for definition of Improvement	Range considered in calculation of absolute Percent Change from Baseline	Level of Improvement compared to Baseline	Level Score
PGA (see 9.11.2.1)	Item "Global Disease Activity/Physician Global Activity" from the MYOSITIS DISEASE ACTIVITY ASSESSMENT TOOL form	Negative change	10	Worsening to 5% improvement	0
				>5% to 15% improvement	7.5
				>15% to 25% improvement	15
				>25% to 40% improvement	17.5
				>40% improvement	20
PtGA (see 9.12.1)	Value directly available in external data transfer	Negative change	10	Worsening to 5% improvement	0
				>5% to 15% improvement	2.5
				>15% to 25% improvement	5
				>25% to 40% improvement	7.5
				>40% improvement	10
Manual Muscle Testing (MMT)-8 (see 9.11.3)	Item "MMT8 score (0 - 150)" from the MANUAL MUSCLE TESTING-8 (mmt8) form	Positive change	150	Worsening to 2% improvement	0
				>2% to 10% improvement	10
				>10% to 20% improvement	20
				>20% to 30% improvement	27.5
				>30% improvement	32.5
Health Assessment Questionnaire-Disability Index (HAQ-DI) (see 9.12.2)	To be derived from external data transfer: For each of the 8 sections, determine the worst score within the section. HAQ-DI=(sum of the 8 scores)/8	Negative change	3	Worsening to 5% improvement	0
				>5% to 15% improvement	5
				>15% to 40% improvement	7.5
				>40% improvement	10
Most abnormal muscle-associated enzymes		Negative change		Worsening to 5% improvement	0
				>5% to 15% improvement	2.5
				>15% to 25% improvement	5

Core Set Measure	Data source	Direction for definition of Improvement	Range considered in calculation of absolute Percent Change from Baseline	Level of Improvement compared to Baseline	Level Score
	Absolute value in external data for the enzyme ¹ with the highest ratio (absolute value/ULN) at baseline		15 times the upper limit of normal (ULN) for Creatine Kinase, 6 times the ULN for Aldolase, and 3 times the ULN for Lactate Dehydrogenase, Aspartate Aminotransferase, and Alanine Transaminase (Aggarwal 2017)	>25% improvement	7.5
Extramuscular activity (see 9.11.2.2)	Item "Extramuscular Global Assessment" from the MYOSITIS DISEASE ACTIVITY ASSESSMENT TOOL form	Negative change	10	Worsening to 5% improvement	0
				>5% to 15% improvement	7.5
				>15% to 25% improvement	12.5
				>25% to 40% improvement	15
				>40% improvement	20

¹ Among creatinine Kinase, Lactate Dehydrogenase, Aspartate Aminotransferase, Alanine Aminotransferase and Aldolase.

It is important to note that when assigning the "level of improvement" that the direction of the test has to be considered, e.g., a negative percentage change is considered an improvement for PtGA, but not for MMT-8.

9.11.2 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.

9.11.2.1 Global Disease Activity/Physician Global Activity (PGA)

PGA is an assessment of overall global disease activity by the physician that will be taken from Myositis Disease Activity Assessment Tool (MDAAT) using a 10-cm VAS scale (item “Global Disease Activity/Physician Global Activity” from the MYOSITIS DISEASE ACTIVITY ASSESSMENT TOOL form).

9.11.2.2 Extramuscular Activity Assessment

An assessment of extramuscular activity assessment will be taken from Myositis Disease Activity Assessment Tool (MDAAT) using a 10-cm VAS scale (item “Extramuscular Global Assessment” from the MYOSITIS DISEASE ACTIVITY ASSESSMENT TOOL form).

9.11.3 Manual Muscle Testing (MMT)-8 Score

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.

The total score for bilateral testing (item “MMT8 score (0 - 150)” from the MANUAL MUSCLE TESTING-8 (mmt8) form) will be considered in the derivation of the TIS.

9.11.4 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.

9.11.5 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.

■ CCI [REDACTED]

■ [REDACTED]

[REDACTED]

10 Study Participants

The subsections in this section include specifications for reporting participant disposition and study intervention/study discontinuations. Additionally, procedures for reporting protocol deviations are provided.

Unless otherwise specified, all the related outputs will be provided for both the primary analysis and the secondary analysis; all the data from Screening will be considered and all the visits performed will be presented in summary tables and listings.

10.1 Disposition of Participants and Discontinuations

The number and percentage of participants in each of the below disposition categories will be presented separately by intervention groups and overall. Percentages will be presented with respect to the number of randomized participants.

- Total number of participants screened (i.e., participants who gave informed consent)
- Number of participants who discontinued the study prior to randomization overall and grouped by the main reason (Subject did not meet all eligibility criteria, Withdrawal by subject, Progressive disease, Adverse event, Lost to follow-up, Death, Other)
- Number and percentage of randomized participants.

The end of study intervention status will be summarized by:

- Number and percentage of randomized participants who did not receive any dose of study intervention
- Number and percentage of randomized participants with ongoing study intervention during the DBPC period.
- Number and percentage of randomized participants who completed the study intervention during the DBPC period based on ENPATORAN/PLACEBO TERMINATION (tterm1) form.
- Number and percentage of randomized participants who discontinued the study intervention (overall and by primary reason) during the DBPC period based on ENPATORAN/PLACEBO TERMINATION (tterm1) form.
- Number and percentage of randomized participants with ongoing study intervention during the OLE period.

- Number and percentage of randomized participants who completed the study intervention during the OLE period based on ENPATORAN TERMINATION (Open Label Extension) (tterm2) form.
- Number and percentage of randomized participants who discontinued the study intervention (overall and by primary reason) during the OLE period based on ENPATORAN TERMINATION (Open Label Extension) (tterm2) form.

The end of study status will be summarized by:

- Number and percentage of randomized participants still on-study
- Number and percentage of randomized participants who completed or prematurely discontinued the study after randomization, grouped by main reason.

A listing of participants including their date and version of informed consent, the reason for not continuing beyond screening and the date of randomization will be provided. A listing of participants with their end of study intervention status for the DBPC period (based on ENPATORAN/PLACEBO TERMINATION [tterm1] form) and their end of study intervention status for the OLE period (based on ENPATORAN TERMINATION (Open Label Extension) [tterm2] form), and with the associated reason(s). Moreover, a listing of participants with their end of study status and with the associated reason(s) will be provided.

Additionally, the number of participants screened, and included in each analysis set will be provided overall, by region (North America, Western Europe, Eastern Europe, South America, Asia, Rest of the world), by country within region and by site, and a listing of participants excluded from at least one analysis set will be provided. See the analysis sets considered in the primary analysis (DBPC analysis) and in the secondary analysis (OLE) in [Section 8.1](#).

The results of the randomization algorithm (according to IWRS) will be summarized as follows for the primary analysis:

- Number and percentage of randomized participants overall, by region (North America, Western Europe, Eastern Europe, South America, Asia, Rest of the world), by country within region
- Number and percentage of randomized participants by randomization strata (source: IWRS)
- Number and percentage of randomized participants by randomization strata (source: eCRF)
- Cross tabulation: participants randomized (placebo, enpatoran 100 mg BID) vs. treated (placebo, enpatoran 100 mg BID)

Assessment of COVID-19 Impact

For the assessment of COVID-19 impact on this study, an overview table will be presented by study intervention group with the following information:

- Participants with at least one COVID-19 impact
- Participants with at least one COVID-19 impact in the following categories: AEs, death, protocol deviations, missed dose for drug administration, dose interruption for drug administration, missed assessments (VS, ECG, MMT-8, MDAAT, central laboratory [hematology, chemistry, aldolase], PtGA, HAQ-DI, CCI), missed visits, tele visits replacing on-site visits, treatment discontinuation, study discontinuation.
- Number of participants with missed assessments, missed visit (VS, ECG, MMT-8, MDAAT, central laboratory [hematology, chemistry, aldolase], PtGA, HAQ-DI, CCI), tele-visits replacing on-site visits (1 / 2 / 3 / >3)

A listing of COVID-19 impact will also be provided.

Disposition of PRO Questionnaires

The disposition of PRO questionnaires will be described (by study group intervention) for PtGA, CCI and HAQ-DI separately at Baseline at start of DBPC, DBPC Week 12, and DBPC Week 24, OLE Day 1, OLE Week 12 and OLE Week 24, and also at DBPC Week 4, DBPC Week 8, DBPC Week 16, DBPC Week 20 for PtGA and HAQ-DI, as described below:

- Number of randomized participants for whom the visit is expected, i.e., the number of participants who are still ongoing in the study at the time of the visit.
- Number and percentage of randomized participants who returned the questionnaire at the visit as expected (compliance rate using all expected PRO questionnaires in the denominator)

$$\% \text{ Compliance} = 100 \times \frac{\text{number of participants who returned the PRO questionnaire}}{\text{number of participants for whom a PRO questionnaire is expected}}$$

A questionnaire is considered returned if at least one item from the questionnaire is answered, and number of participants for whom a PRO questionnaire is expected does correspond to the number of participants who are still ongoing in the study at the time of the visit.

- Number and percentage of randomized participants with an evaluable questionnaire at the visit (completion rate using all expected PRO questionnaires in the denominator)

$$\% \text{ Completion} = 100 \times \frac{\text{number of participants with an evaluable PRO questionnaire}}{\text{number of participants for whom a PRO questionnaire is expected}}$$

A questionnaire is considered evaluable if PRO scores can be derived according to scoring manual for at least one subscale, and number of participants for whom a PRO questionnaire is expected does correspond to the number of participants who are still ongoing in the study at the time of the visit.

Reasons for non-completion and non-compliance of PtGA, CCI HAQ-DI will also be described (by study group intervention) at Baseline at start of DBPC, DBPC Week 12, and DBPC Week 24, OLE Day 1, OLE Week 12 and OLE Week 24, and also at DBPC Week 4, DBPC Week 8, DBPC Week 16, DBPC Week 20 for PtGA and HAQ-DI, as follows:

- Number and percentage of randomized participants with non-expected questionnaire at the visit by reason (i.e. who are not ongoing in the study at the time of the visit) – reasons for non-compliance:
 - Death
 - Lost to follow-up
 - Withdrawal by subject
 - Other reason for study termination
- Number and percentage of randomized participants with missing questionnaire at the visit by reason while expected – reasons for non-completion:
 - Subject felt too ill
 - Clinician or nurse felt the subject was too ill
 - Subject felt it was inconvenient
 - Subject felt it takes too much time
 - Subject felt it was not relevant
 - Subject felt it was a violation of privacy
 - Subject did not understand the actual language
 - Administrative failure to distribute the questionnaire to the subject
 - Subject unable to come to site
 - Site was closed
 - Investigator decision
 - Subject did not come for unknown reasons
 - Other
 - Non-completion due to COVID-19 (Yes, No)

10.2 Protocol Deviations / Exclusion from Analysis Sets

10.2.1 Important Protocol Deviations

Important protocol deviations (IPDs) are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

All protocol deviations (important and non-important) will be documented in SDTM datasets whether identified through site monitoring, medical review or programming.

Important protocol deviations or important events that might have an effect on PK include, but may not be limited to the following:

- Adverse events, diarrhea, etc. (these instances will be discussed on a case-by case basis)
- Vomiting after administration following oral dosing (these instances will be discussed in alignment with applicable regulatory guidelines on a case-by-case basis)
- Sample processing errors that may lead to inaccurate bioanalytical results
- Inaccurate dosing or dosing errors (e.g., dose administration delayed, dose change, or missed doses)
- Pre-dose or trough sample collected after the actual dosing
- Concomitant medication, vitamins, dietary or herbal supplements

Should one or more of these events be available at the Data Review Meeting, its implication for PK evaluation will be discussed and agreed amongst relevant study team members (e.g., Sponsor Clinical Pharmacology/Biostatistics/Clinical Pharmacokinetics & Pharmacodynamics team representative). Appropriate action will be taken such as flagging individual values to be excluded from analysis.

A frequency table of important protocol deviations will be provided based on the FAS for the primary analysis and FAS-OLE for the secondary analysis, by study intervention group. This table will present the number of participants with at least one important protocol deviation overall, per category and per deviation description.

A listing of participants with important protocol deviations will be provided.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

A listing of participants excluded from the PK analysis set and/or PD analysis set for the primary analysis, and a listing of participants excluded from the PK-OLE analysis set and/or PD-OLE analysis set for the secondary analysis, including the associated reason(s) will be provided.

11 Demographics and Other Baseline Characteristics

If not stated otherwise, the following analyses will be performed based by study intervention group and overall, on the FAS for the primary analysis and on the FAS-OLE for the secondary analysis.

11.1 Demographics

Demographic characteristics and physical measurements will be summarized descriptively using the following information from the Screening/Baseline visit eCRF pages.

The following demographic characteristics will be included:

- Sex: male, female, undifferentiated
- Race:
 - American Indian or Alaska Native
 - Asian
 - Chinese, Japanese, Korean, Other Asian
 - Black or African American
 - Native Hawaiian or Other Pacific Islander
 - White
 - More than one race
 - Any combination
 - Other
 - Not permitted per local regulation
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not permitted per local regulation
- Age (years) as collected in eCRF
- Age categories:
 - ≤ 45 years
 - > 45 - ≤ 65 years,
 - > 65 years
- Pooled Region:
 - North America, Western Europe and Eastern Europe
 - Asia
 - Central/South America and Rest of the World
- EEA (European Economic Area): Yes, No

An individual participant data listing of demographic will also be provided.

11.2 Medical History

The medical history will be summarized from the “Medical History Details” eCRF page, using the most recent MedDRA version at time of database lock, preferred term as event category and system organ class (SOC) body term as body system category. Each participant will be counted only once within each PT or SOC.

Medical history will be displayed by a frequency table ordered by primary SOC and PT in alphabetical order. An individual participant data listing of medical history will also be provided.

11.3 Other Baseline Characteristics

Information on disease characteristics collected at Baseline at start of DBPC will be summarized. Summary statistics will be presented for:

Disease history:

- 1) Disease diagnosis:
 - Classification
 - Definite Idiopathic Inflammatory Myopathies
 - Probable Idiopathic Inflammatory Myopathies
 - Possible Idiopathic Inflammatory Myopathies
 - Subgroup
 - Participants with rash at baseline at start of DBPC (CDASI-A ≥ 7): CDASI-A < 14 , or ≥ 14 at baseline at start of DBPC
 - All participants: MMT-8 ≥ 80 to 136, or > 136 at baseline at start of DBPC
 - Disease subtype: DM, PM
 - Patients with rash defined as a value for CDASI-A at baseline ≥ 7 at start of DBPC period (yes, no)
 - Pathological evidence of active myositis in muscle biopsy within 6 months prior to Screening (yes, no)
 - Evidence of active myositis by electromyography within the last 6 months prior to Screening (yes, no)
 - Evidence of active myositis by MRI within the last 6 months prior to Screening (yes, no)
 - Time since documented diagnosis (years) for DM and PM separately
- See [Section 9.10](#) for handling of incomplete dates.

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Background therapy at Baseline:

Based on the “CORTICOSTEROID MEDICATION DETAILS” form.

- 1) Oral CS use at Baseline (yes, no)
- 2) Daily prednisone-equivalent CS dose at Baseline (mg) as a continuous variable (see [appendix 18.2](#) for derivation)
- 3) Daily prednisone-equivalent CS dose at Baseline (mg) categorized as below:
 - $< 10, \geq 10$
 - $< 6, \geq 6 - < 7.5, \geq 7.5 - < 10, \geq 10 - < 15, \geq 15 - < 20, 20, > 20$
- 4) Number and percentage of participants taking antimalarials at Baseline (yes, no)
Use of antimalarials will be derived at Day 1 using concomitant medications data with class = “Antimalarials”, ATC code level 3 = P01B.

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will be summarized descriptively at screening in the PD2 analysis set: in screening failures, enrolled participants and all participants. An individual participant data listing will also be provided.

An individual participant data listing of disease history will also be provided.

12 Therapies/Procedures

The following analyses will be performed based on the FAS for the primary analysis and on the FAS-OLE for the secondary analysis by study intervention group. At the secondary analysis after OLE period, only outputs related to concomitant medications will be provided.

Concomitant medications are medications, other than study intervention, which are taken by participants any time during the on-treatment period (see [section 9.8](#)).

Concomitant Corticosteroids are corticosteroids which are taken by participants any time during the on-treatment period (see [section 9.8](#)), based on the “CORTICOSTEROID MEDICATION DETAILS” form.

Previous medications are medications other than study intervention which started before the first administration of study intervention.

A medication may be classified as both concomitant and previous. The respective flags will be derived based on start and end date (see [section 9.10](#) for derivation).

Previous and concomitant medications will be summarized by the number and percentage of participants. Preferred term within ATC Classification code level 2 will be tabulated as given from the WHO-DD dictionary most current version.

If any previous or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes.

The summary tables will be sorted by decreasing frequency of drug class and decreasing frequency of preferred term in a given drug class. In case of equal frequency regarding ATC classification level 2 or preferred term, alphabetical order will be used.

In case any specific medication has an uncoded preferred term or an uncoded ATC classification level 2 coded term or, it will be summarized under “Unknown” category. Each participant will only be counted once, even if he/she received the same medication at different times.

The following individual participant data listings will be provided:

- Previous and concomitant medications
- Corticosteroid medication
- Concomitant procedures
- Chest imaging at screening
- Serum virology at screening
- Quantiferon tuberculosis test at screening
- SARS-Cov-2 test at screening
- Reflex testing for HBV DNA
- Exercise regimen.

13 Study Intervention: Compliance and Exposure

The following analyses will be performed based on SAF for the primary analysis and on the SAF-OLE for the secondary analysis, by study intervention group. They will be conducted for the primary analysis after the DBPC period and the secondary analysis after the OLE period. The summary statistics will be presented for treatment during the DBPC period, and for treatment during the OLE period and the (DBPC and OLE) periods for the secondary analysis.

All dosing calculations and summaries will be based on eDiary data and “eDiary dose change details (exposedrt1)” eCRF page and “OLE eDiary dose change details (ole_exposedrt1)” for participants having used an eDiary, and will be based on “Enpatoran/placebo administration details (exposedrt2)” eCRF page and “OLE enpatoran administration (ole_exposure)” eCRF page for participants having used a paper diary.

The duration of exposure to study drug in weeks will be calculated according to the following formula:

Treatment duration (weeks) = (date of last administration received – date of first administration received + 1)/7

Treatment duration will be summarized as a continuous variable and according to the following categories: (≤ 2 weeks, $> 2 - \leq 10$ weeks, $> 10 - \leq 14$ weeks, $> 14 - \leq 22$ weeks, > 22 weeks) for the DBPC or the OLE period, and (≤ 2 weeks, $> 2 - \leq 10$ weeks, $> 10 - \leq 14$ weeks, $> 14 - \leq 22$ weeks, $> 22 - \leq 30$ weeks, $> 30 - \leq 38$ weeks, > 38 weeks) for the (DBPC + OLE) periods.

Cumulative dose (mg) is defined as the sum of all actual doses of study intervention taken during the study and will be summarized for the active study intervention group as a continuous variable. A participant may have different dosing intervals. Total cumulative dose will then be computed as the sum of the cumulative doses received during each constant-dosing interval. Cumulative dose received during the dosing interval will be computed as:

- (date of last dose – date of first dose + 1) x number of tablets taken x r x 25, where r is the fraction of tablets containing enpatoran 25 mg for the kits dispensed during this interval: r=0 for placebo, r=1 for enpatoran 100 mg BID

Compliance (%) with study intervention will also be summarized. It will be computed as follows:

$$Compliance = 100 \times \left(\frac{N_1}{8 \cdot N_2} \right)$$

Where:

N1 = total number of tablets taken during the study,

N2 = date of last dose – date of first dose + 1.

It will also be summarized using the following categorization: $< 80\%$, $80\% - 125\%$, $> 125\%$.

The following by-participant data listings will be provided:

- Listing of start/end dates of each constant-dosing interval together with the number of tablets ingested during that interval and reason for change in dose.
- Listing of start date and time of administrations on site, dose timepoint, date and time of last and first meal before and after administration respectively.
- Listing with exposure time, cumulative dose, and compliance.

14 Efficacy Analyses

The following analyses will be performed by study intervention group. Unless otherwise specified, the visit window algorithm described in [Section 9.7](#) will be applied to all efficacy assessments.

14.1 Primary Estimand: Total Improvement Score at DBPC Week 24

The primary, supportive and subgroup analyses of this estimand will be conducted at the time of the primary analysis after the DBPC period.

14.1.1 Primary Objective: Derivation and analysis of the primary estimand

The primary efficacy variable is the ACR/EULAR mean Total Improvement Score (TIS) at DBPC Week 24 of the DBPC part of the study.

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Descriptive Analysis:

Descriptive statistics on the TIS at DBPC Week 24 will be provided by study intervention group.

Means for the TIS and corresponding 95% CIs will be presented by study intervention group. Similarly, the mean differences (and 95% CI) between enpatoran and placebo will be provided. 95% CIs will be based on a parametric method (t-distribution).

14.1.2 Supplementary Analyses of the Primary Estimand

Modeling of TIS with Corticosteroids dose and accounting for covariates will be performed. A linear mixed model for repeated measures will have TIS score as dependent variable, study intervention group, time (weeks, as continuous variable), daily prednisone-equivalent CS dose (mg), and covariates as fixed factors. The linear mixed model will have a random intercept for each subject.

Covariates include:

- Disease type: DM, or PM
- Disease severity
 - CDASI-A <14, or ≥ 14 at baseline at start of DBPC
 - MMT-8 ≥ 80 to 136, or >136 at baseline at start of DBPC
- Other important participants characteristics
 - Daily prednisone-equivalent CS dose at Baseline at start of DBPC (mg) categorized as: < 5, ≥ 5 to ≤ 10 , > 10.

Least square means (and 95% CIs) of TIS in each treatment group at DBPC Week 24 will be displayed. Least square means (and 95% CI) for the treatment difference at DBPC Week 24 and the p-value will also be displayed.

14.1.3 Subgroup Analyses of the Primary Estimand

Descriptive statistics on the TIS at DBPC Week 24, mean for the TIS (and 95% CI based on a parametric method (t-distribution)), mean of the differences (and 95% CI based on a parametric method (t-distribution)) between enpatoran and placebo will also be provided in the following subgroups:

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

14.2 Secondary Estimands

14.2.1 Total Improvement Score Responder

Attributes of the estimand are described in the table below.

Endpoint(s)	• 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(s)	DM and PM patients
Treatment	Enpatoran compared to placebo
CCI [REDACTED]	
Population-level summary measure	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

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Frequency and percentage of participants having at least 1 of the 4 intercurrent event will be summarized at Baseline at start of DBPC to and including DBPC Week 24 for the primary analysis, and to and including OLE Week 24 for the secondary analysis.

Bar charts of percentage of participants reaching the TIS responses (≥ 20 , ≥ 40 , ≥ 60) by post-baseline visits (from DBPC Week 4 up to and including OLE Week 24) and by study intervention group will also be provided.

14.2.2 Total Improvement Score and IMACS Core Set Measures

Attributes of the estimand are described in the table below.

Endpoint(s)	- TIS at each visit from Week 4 up to and including Week 24 - Physician global activity (PGA) at visit from Week 4, up to and including Week 24 - Patient global activity (PtGA) at each visit from Week 4, up to and including Week 24 - MDAAT extra muscular component 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
Population(s)	DM and PM patients
Treatment	Enpatoran compared to placebo
CCI	
Population-level summary measure	Difference of means and 95% CI

A tertiary objective of the study is to evaluate the efficacy in DM and PM participants during the OLE period (according to treatment received during DBPC). Hence the analyses described below will also be performed for the secondary analysis.

Descriptive Analysis

Absolute value of TIS, and absolute value, absolute change and percent change from baseline in PGA, PtGA, MDAAT extra muscular component, MMT-8 score and HAQ-DI will be summarized using standard statistics at Baseline and each post-baseline visit (from DBPC Week 4, up to and including OLE Week 24) by study intervention group, and in the following subgroups for the primary analysis:

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

The difference between enpatoran and placebo for the absolute change (and 95% CI based on a parametric method (t-distribution)), and the difference between enpatoran and placebo for the relative change (and 95% CI based on a parametric method (t-distribution)) will also be provided.

Percent change from baseline in most abnormal muscle enzyme will be summarized using standard statistics at each post-baseline visit (from DBPC Week 4, up to and including OLE Week 24) by study intervention group, and in the following subgroups for the primary analysis:

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

The difference between enpatoran and placebo for the relative change (and 95% CI based on a parametric method (t-distribution)) will also be provided.

Boxplots of TIS, PGA, PtGA, MDAAT extra muscular component, MMT-8 score and HAQ-DI by visit (at baseline [except for TIS], and for each post-baseline visit (from DBPC Week 4 up to and including OLE Week 24) and by study intervention group will also be provided.

Absolute change and percent change from baseline in PGA, PtGA, MDAAT extra muscular component, MMT-8 score and HAQ-DI at each visit (from DBPC Week 4 up to and including OLE Week 24) will be displayed using line plots of mean and SD bars.

Percent change from baseline in most abnormal muscle enzyme at each visit (from DBPC Week 4, up to and including OLE Week 24) will be displayed using line plots of mean and SD bars.

Individual participant data listings of TIS, PtGA, MDAAT, MMT-8 and HAQ-DI will be provided.

14.2.3 IMACS Responder

A participant is defined as a IMACS Responder if 3 of any 6 IMACS CSMs have been improved by $\geq 20\%$, with no more than 2 IMACS CSMs worse by $\geq 25\%$ (which cannot be MMT-8, i.e. MMT-8 did not worsen).

Endpoint(s)	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, i.e. MMT-8 did not worsen)
Population(s)	DM and PM patients
CCI	
Population-level summary measure	Number and % of responders; difference from placebo with 95% CI

A tertiary objective of the study is to evaluate the efficacy in DM and PM participants during the OLE period (according to treatment received during DBPC). Hence the analyses described below will also be performed for the secondary analysis.

Descriptive Analysis

Descriptive statistics on the occurrence of IMACS responder will be provided by study intervention group and post-baseline visit (from DBPC Week 4 up to and including OLE Week 24). If the IMACS response cannot be assessed or if participant has met any of the intercurrent events before the visit, then the participant will be considered as non-responder at that visit. Differences in responder rate between enpatoran and placebo will be presented by study intervention group, and in the following subgroups for the primary analysis:

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

The corresponding 95% CIs will be based on Miettinen and Nurminen method ([Miettinen and Nurminen, 1985](#)).

Bar charts of percentage of IMACS responders by visit (from DBPC Week 4 up to and including OLE Week 24) and by study intervention group will also be provided.

14.2.4 Cutaneous Dermatomyositis Area and Severity Index (CDASI) and Investigator's Global Assessment (IGA) skin activity

Endpoint(s)	- Change and percent change from baseline in CDASI-A and CDASI-D at each visit from Week 4, up to Week 24. See Section 9.11.4 - Change and percent change from baseline in IGA skin activity at each visit from Week 4, up to Week 24. See Section 9.11.5
Population(s)	DM and PM patients with rash
Treatment	Enpatoran compared to placebo
CCI	
Population-level summary measure	Difference of means and confidence intervals

Descriptive Analysis

The following analyses will be performed in the FAS_rash for the primary analysis, and in the FAS_rash-OLE for the secondary analysis.

Absolute value, absolute change and percent change from baseline in CDASI-A, CDASI-D and IGA skin activity will be summarized using standard statistics at Baseline at baseline at start of DBPC and, each post-baseline visit (from DBPC Week 4, up to and including OLE Week 24) by study intervention group, and in the following subgroups for the primary analysis:

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

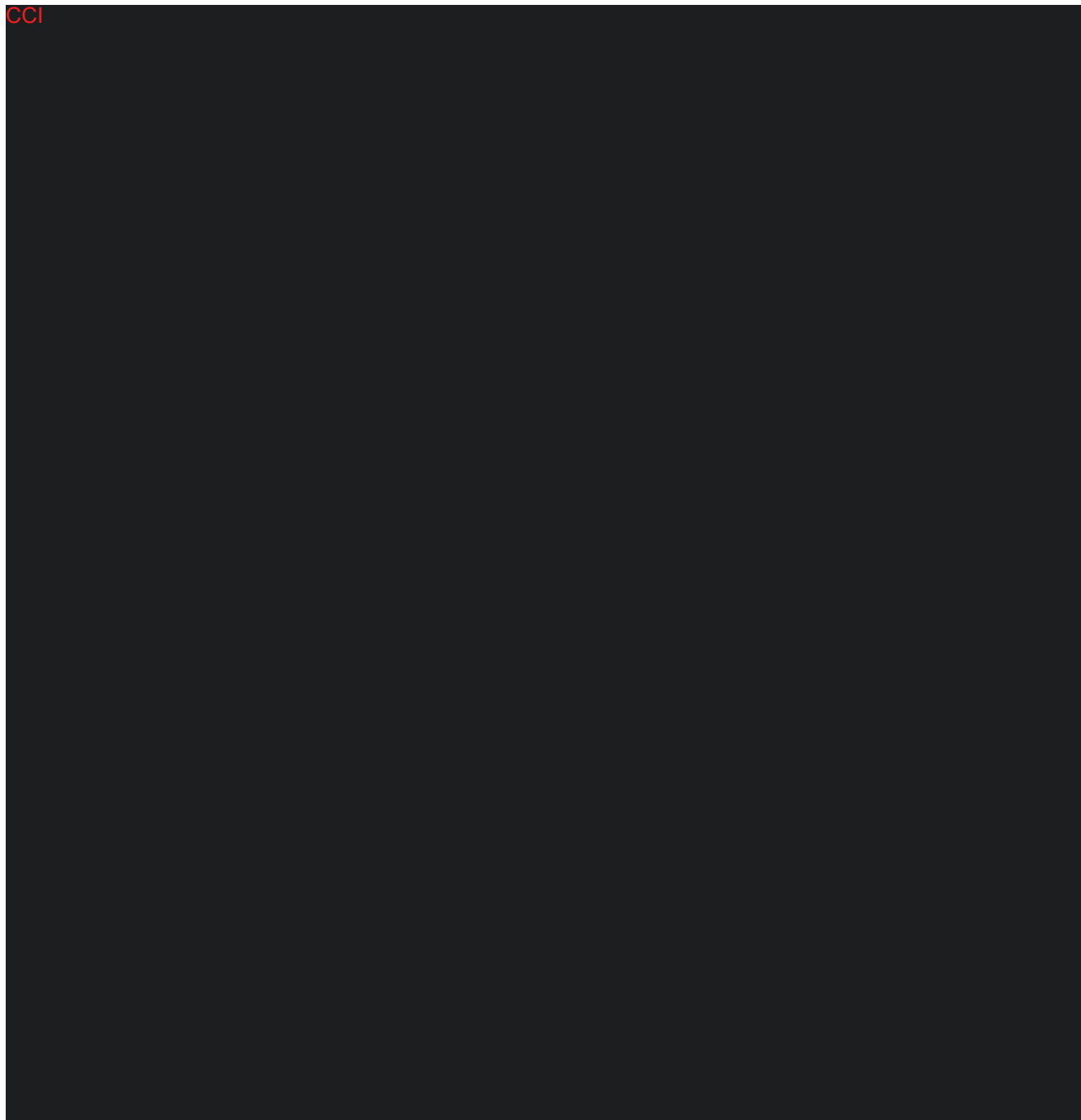
The difference between enpatoran and placebo for the absolute change (and 95% CI based on a parametric method (t-distribution)), and the difference between enpatoran and placebo for the relative change (and 95% CI based on a parametric method (t-distribution)) will also be provided.

Boxplots of CDASI-A, CDASI-D and IGA skin activity by visit (at baseline at start of DBPC, and from DBPC Week 4 up to and including OLE Week 24) and by study intervention group will also be provided.

Absolute change and percent change from baseline in CDASI-A, CDASI-D and IGA skin activity at each post-baseline visit (from DBPC Week 4 up to and including OLE Week 24) will be displayed using line plots of mean and SD bars.

Individual participant data listings will be also provided.

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15 Safety Analyses

Safety analyses will be performed according to the as-treated principle on the SAF for the primary analysis and on the SAF-OLE for the secondary analysis, by study intervention group unless otherwise specified.

15.1 Adverse Events

Some outputs will be split by period, or will be regarding the OLE period only. In that case, an adverse event will be considered as being during the DBPC period if the start date is prior to the first dose of study intervention in the OLE period. On the other hand, an adverse event will be considered as being during the OLE period if:

- It started during DBPC period and is still ongoing at the start date of the first dose of study intervention in the OLE period, OR
- If the start date of the event is after the first dose of study intervention in the OLE period.

(TEAEs are defined as follows for each period:

- TEAEs during the DBPC period are the adverse events with onset or worsening dates occurring on or after the first dose of study intervention during the DBPC period, and prior to the first dose of study intervention during the OLE period.
- TEAEs during the OLE period are the adverse events with onset or worsening dates occurring on or after the first dose of study intervention during the OLE period.
- TEAEs during the DBPC period or the OLE period are the adverse events with onset or worsening dates occurring on or after the first dose of study intervention during the DBPC period.

This also includes AEs ongoing at Baseline at start of DBPC, which first improve under study intervention and then worsen irrespective of baseline. AEs with changes in toxicity grade, seriousness or outcome of AEs are recorded as separate entries in the eCRF with associated end and start dates (start date equals end date of previous entry, supported in eCRF by “AECHGID” in SUPPAE). Records of the same AE will be considered as one event in the analysis. If the severity or seriousness of the reported event worsens after start of treatment, the TEAE flag will be re-evaluated for the worse and the subsequent records as per the TEAE definition. These events will be kept as separate records in the database in order to maintain the full detailed history of the events. The overall outcome of the AE is the outcome of the last event in the sequence. When such AEs are listed, start, end date and outcome should be provided together with change date, toxicity grade and seriousness per episode.

AEs will be summarized using the latest version of MedDRA at the time of the database lock with PT as event category and MedDRA primary SOC body term as body system category.

Analysis by severity will be performed according to NCI-CTCAE version 5.0. In case a participant has events with missing and non-missing grades, the maximum of the non-missing grades will be used. No imputation of missing grades will be performed.

Incomplete AE-related dates will be handled as specified in [section 9.10](#).

All analyses described in this section 15.1 will be based on TEAEs if not otherwise specified.

Unless otherwise specified, TEAEs will be summarized by number and percentage of participants with at least one TEAE in the category of interest, by study intervention group, primary SOC in alphabetical order, and PT in decreasing incidence overall.

Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

15.1.1 All Adverse Events

The following tables will be provided:

- Overview of TEAEs by study intervention group, including:
 - TEAEs
 - TEAEs, Grade ≥ 2 , Grade ≥ 3 , Grade ≥ 4
 - Related TEAEs
 - Related TEAEs, Grade ≥ 2 , Grade ≥ 3 , Grade ≥ 4
 - Serious TEAEs
 - Non-serious TEAEs
 - Related Serious TEAEs
 - TEAEs leading to death
 - Related TEAEs leading to death
- TEAEs by SOC and PT
- TEAEs by SOC and PT and worst grade (Any Grade, Grade ≥ 2 , Grade ≥ 3 , Grade ≥ 4)
- Related TEAEs by SOC and PT
- Related TEAEs by SOC and PT and worst grade (Any Grade, Grade ≥ 2 , Grade ≥ 3 , Grade ≥ 4)
- TEAEs excluding Serious Adverse Events (SAEs), with frequency $\geq 5\%$ in any study intervention group by SOC and PT. “Number of subjects with at least one event” represents the number of participants with at least one AE among AEs where frequency is $\geq 5\%$ in at least one study intervention group.

The overview table of TEAEs, the table of TEAEs by SOC and PT and the table of related TEAEs by SOC and PT will also be performed in the following subgroups:

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

The following individual participant data listings will be provided:

- All AEs
- TEAEs
- Trial Drug Related TEAEs
- Grade ≥ 3 and serious TEAEs
- TEAEs leading to permanent Treatment Discontinuation
- Adverse Events of Special Interest (AESIs).

15.1.2 Adverse Events Leading to Discontinuation of Study Intervention

The overall summary of TEAEs leading to discontinuation of study intervention will include the frequency (number and percentage) of participants with each of the following, split by study intervention group:

- TEAEs leading to permanent discontinuation (drug withdrawn)
- Related TEAEs leading to permanent discontinuation (drug withdrawn)
- TEAEs leading to temporary discontinuation (drug interrupted)
- Related TEAEs leading to temporary discontinuation (drug interrupted)

A frequency table of TEAE leading to permanent discontinuation of study intervention and a frequency table of TEAE leading to temporary discontinuation of study intervention will also be provided by primary SOC in alphabetical order and, within SOC, sorted by PT in decreasing incidence overall.

15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.2.1 Deaths

Death date and reason for death are collected on the “DEATH” CRF form.

A participant data listing including date and reason of death, PT of AEs with fatal outcome together with selected dosing information (date of first/last administration and number of ingested tablets) will be provided.

15.2.2 Serious Adverse Events

The following frequency tables will be prepared for serious TEAEs:

- Incidence of serious TEAEs by SOC and PT
- Incidence of related serious TEAEs by SOC and PT

The tables will also be performed in the following subgroups:

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

A listing of SAEs will also be provided with the relevant information with a flag for SAEs with onset outside the on-treatment period.

15.2.3 Other Significant Adverse Events

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AESI will be identified using the corresponding flag entered in the “Adverse Event” eCRF page. In order to define the category to which they belong, SMQs or primary SOC will be used depending on the AESI (see table below).

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The following tables will be provided:

- TEAEs of special interest by SOC and PT
- TEAEs of special interest by SOC and PT and worst grade (Any Grade, Grade ≥ 2 , Grade ≥ 3 , Grade ≥ 4).

The table of TEAEs of special interest by SOC and PT will also be performed in the following subgroups:

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

15.3 Clinical Laboratory Evaluation

All laboratory values will be reported in SI units. Time window will be applied to laboratory assessments (see [section 9.7](#)).

Laboratory values (including corresponding normal ranges) from the central laboratory will be used for summary statistics and shift tables.

In case both central and local labs are collected, summary statistics will be based on central lab collected data, while summaries of worst post-baseline abnormalities will be based on both local and central laboratory data.

Laboratory results will be graded according to NCI-CTCAE version 5.0. Laboratory parameters which cannot be graded per NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

The definition of baseline measurement is provided in [section 9.2](#).

Values below the detection limit will be imputed by half of the detection limit. If a text value with an “> x” is reported it will be analyzed as +1 significant digit, e.g., “> 7.2 mmol” will be analyzed as 7.3.

Quantitative data (hematology, biochemistry, coagulation and urinalysis) will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) of raw values and absolute changes from baseline at each post baseline visit (from DBPC Week 4 up to and including OLE Week 24), by study intervention group, and in the following subgroups:

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

Qualitative data (hematology, biochemistry and coagulation) based on reference ranges will be described according to the categories (i.e., low, normal, high), by study intervention group, and in the following subgroups:

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

For urinalysis parameters, the classification Normal, Trace/+, ++, +++, +++++ will be used instead.

Abnormalities classified according to NCI-CTCAE toxicity grading version 5.0 will be described using the worst post-baseline grade. Unless otherwise specified, number of participants with missing measurements will be presented as separate category. For those parameters which are graded with two directions of toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (e.g., hypokalemia) grades at Baseline and post-baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (e.g., hyperkalemia), and vice versa. The same applies for non-gradable parameter, and description of changes from Normal/Low to High and Normal/High to Low will be provided, accordingly. The direction of parameters can be found in the MS ADaM template, except for eGFR for which the worst post-baseline value will be considered as the lowest value, and CO₂ for which the worst post-baseline value will be considered in the two directions (both lowest and highest values). eGFR will be derived based on individual participant data.

For **WBC differential counts** (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported. When only percentages are available (this is mainly important for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

$$\text{Derived differential absolute count} = (\text{WBC count}) * (\text{Differential \% value} / 100)$$

If the range for the differential absolute count is not available (only range for value in % is available) then Grade 1 will be attributed to as follows:

- Lymphocyte count decreased:
 - derived absolute count does not meet Grade 2-4 criteria, and
 - % value < % LLN value, and
 - derived absolute count ≥ 800/mm³
- Neutrophil count decreased
 - derived absolute count does not meet Grade 2-4 criteria, and
 - % value < % LLN value, and
 - derived absolute count ≥ 1500/mm³

For **calcium**, CTCAE grading is based on Corrected Calcium and Ionized Calcium (CALCIO), if available. Corrected Calcium is calculated from Albumin and Calcium as follows:

$$\text{Corrected calcium (mmol/L)} = \text{measured total calcium (mmol/L)} + 0.02 (40 - \text{serum albumin [g/L]})$$

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin are used to assess possible drug induced liver toxicity. The ratios of test result over upper limit of normal (ULN) will be calculated and classified for these 3 parameters during the on-treatment period.

Summary of liver function tests will include the categories listed below. The number and percentage of participants with each of the following during the on-treatment period will be summarized by study intervention group:

- $\text{ALT} \geq 3 \times \text{ULN}$, $\text{ALT} \geq 5 \times \text{ULN}$, $\text{ALT} \geq 10 \times \text{ULN}$, $\text{ALT} \geq 20 \times \text{ULN}$
- $\text{AST} \geq 3 \times \text{ULN}$, $\text{AST} \geq 5 \times \text{ULN}$, $\text{AST} \geq 10 \times \text{ULN}$, $\text{AST} \geq 20 \times \text{ULN}$
- $(\text{ALT or AST}) \geq 3 \times \text{ULN}$, $(\text{ALT or AST}) \geq 5 \times \text{ULN}$, $(\text{ALT or AST}) \geq 10 \times \text{ULN}$, $(\text{ALT or AST}) \geq 20 \times \text{ULN}$
- $\text{TBILI} \geq 2 \times \text{ULN}$
- Concurrent $\text{ALT} \geq 3 \times \text{ULN}$ and $\text{TBILI} \geq 2 \times \text{ULN}$
- Concurrent $\text{AST} \geq 3 \times \text{ULN}$ and $\text{TBILI} \geq 2 \times \text{ULN}$
- Concurrent $(\text{ALT or AST}) \geq 3 \times \text{ULN}$ and $\text{TBILI} \geq 2 \times \text{ULN}$
- Concurrent $(\text{ALT or AST}) \geq 3 \times \text{ULN}$ and $\text{TBILI} \geq 2 \times \text{ULN}$ and $\text{ALP} > 2 \times \text{ULN}$
- Concurrent $(\text{ALT or AST}) \geq 3 \times \text{ULN}$ and $\text{TBILI} \geq 2 \times \text{ULN}$ and $\text{ALP} \leq 2 \times \text{ULN}$ or missing

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, i.e., a participant with an elevation of $\text{AST} \geq 10 \times \text{ULN}$ will also appear in the categories $\geq 5 \times \text{ULN}$ and $\geq 3 \times \text{ULN}$. Liver function elevation and possible Hy's Law cases will be summarized using frequency and percentage.

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In addition, a listing of all TBILI, ALT, AST and ALP values for participants with a post-baseline $\text{TBILI} \geq 2 \times \text{ULN}$, $\text{ALT} \geq 3 \times \text{ULN}$ or $\text{AST} \geq 3 \times \text{ULN}$ will be provided.

Analysis for Parameters with NCI-CTCAE Grade Available

The laboratory toxicities will be tabulated using descriptive statistics (number of participants and percentages) during the on-treatment period. Grade 0 is not defined per NCI-CTCAE but will be used in derivations for simplicity to indicate that evaluable measurements are available. Laboratory values within normal range but considered grade 1 according to NCI-CTCAE will not be graded 1 (Grade 0, instead).

- A summary table of laboratory parameters by NCI-CTCAE grade will include number and percentage of participants with at least one value of Grade ≥ 0 , Grade ≥ 3 , Grade ≥ 4 during the on-treatment period.
- A shift table will summarize baseline NCI-CTCAE grade versus the worst on-treatment NCI-CTCAE grade. The highest NCI-CTCAE grade during the on-treatment period is considered as the worst grade for the summary.

In case of gradings involving baseline measurements (parameters identified with a start [*] below) for the identification of grades during the on-treatment period, the shift table will present baseline normal and abnormal. Normal will include measurements below and within normal range (direction increase), or measurements within and above normal range (direction decrease). In case of missing baseline values, the post-baseline grades will be generated assuming the baseline was normal.

- A shift table will summarize baseline status (normal/abnormal) versus the worst post-baseline NCI-CTCAE grade. The highest NCI-CTCAE grade during the on-treatment period is considered as the worst grade for the summary.

The above analyses apply to hematology and chemistry evaluations which can be graded per NCI-CTCAE:

- Hematology

Hemoglobin (HB) (anemia/ hemoglobin increased), Leukocytes (white blood cell decreased/ leukocytosis), Lymphocytes (lymphocyte count increased/decreased), Neutrophils / Absolute Neutrophils Count (ANC) (neutrophil count decreased), Platelet Count (PLT) (platelet count decreased), Eosinophils * (eosinophilia).

- Coagulation

INR * (INR increased), Activated partial thromboplastin time (aPTT prolonged)

- Serum chemistry

Albumin (hypoalbuminemia), Alkaline Phosphatase * (alkaline phosphatase increased), ALT * (ALT increased), AST (AST increased), Total Bilirubin * (blood bilirubin increased), Creatinine * (creatinine increased), Potassium (hypokalemia/ hyperkalemia), Sodium (hyponatremia/ hypernatremia), Calcium (hypocalcemia/hypercalcemia), Glucose (hypoglycemia/hyperglycemia), Gamma Glutamyl Transferase * (GGT) (GGT increased), eGFR (chronic kidney disease), Lactate Dehydrogenase * (lactate dehydrogenase increased), Creatinine Kinase * (CPK increased).

Analysis for Parameters with NCI-CTCAE Grade not Available

Hematology, chemistry and urinalysis evaluations which cannot be graded per NCI-CTCAE criteria will be summarized as frequency (number and row percentage) of participants as follows:

- Shifts from baseline normal to at least one result above normal during on-treatment period
- Shifts from baseline normal to at least one result below normal during on-treatment period

This applies to the following parameters:

- Hematology
Hematocrit (low/high), Mean Corpuscular Hemoglobin (MCH) (low/high), Mean Corpuscular Volume (MCV) (low/high), monocytes (high), basophils (high), C-reactive Protein (CRP) (high), Erythrocyte Sedimentation Rate (ESR) (high)
- Serum chemistry
Total Protein (low), Blood Urea Nitrogen (high), Aldolase (high)
- Urinalysis
pH (low/high), specific gravity (low/high), glucose (trace/1+, 2+, 3+, 4+), protein (trace/1+, 2+, 3+, 4+), occult blood (trace/1+, 2+, 3+, 4+), ketones (trace/1+, 2+, 3+, 4+), bilirubin (trace/1+, 2+, 3+, 4+), urobilinogen (trace/1+, 2+, 3+, 4+), nitrite (trace/1+, 2+, 3+, 4+), leukocyte esterase (trace/1+, 2+, 3+, 4+)

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The following figures will be provided for hematology, coagulation, serum chemistry parameters,

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- Boxplots of the laboratory values (by study intervention group) by timepoint
 - Boxplots of the change from baseline (by study intervention group) by timepoint
- Where applicable, reference lines for NCI-CTCAE grades should be added to graphical displays.

Listings of laboratory results will be provided for all laboratory parameters:

- Hematology
- Biochemistry
- Urinalysis and microscopic evaluation
- Serum and urine pregnancy test

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The listings will be sorted by study intervention, parameter and assessment date or visit for each participant. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges and NCI-CTCAE grades.

15.4 Vital Signs

Vital sign summaries will include all vital sign assessments during the DBPC period for the primary analysis, and including the OLE period as well for the secondary analysis. All vital sign assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

Time window will be applied to assessments of vital signs (see [section 9.7](#)).

The following vital sign parameters will be summarized using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) for raw values and changes from baseline at each scheduled analysis visit:

- Body temperature (°C)
- Systolic and diastolic blood pressure (mmHg)
- Respiration rate (bpm)
- Pulse rate (beats/min)
- Weight (kg)
- Height (cm) (collected at Screening only)
- BMI (kg/m²) (collected at Screening and End of Treatment only)

$$\text{BMI [kg/m}^2\text{]} = \frac{\text{weight [kg]}}{\text{height[cm]}^2} \times 10000$$

by study intervention group, and in the following subgroups:

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

The maximum changes of vital sign measurements from Baseline will be grouped as follows:

	Baseline Value	Change from Baseline
Body temperature increase	< 37 °C; 37 – < 38 °C; 38 – < 39 °C; 39 – < 40 °C; ≥ 40 °C	< 1 °C, 1 – < 2 °C, 2 – < 3 °C, ≥ 3 °C
Pulse rate increase from baseline	< 100 bpm; ≥ 100 bpm	≤ 20 bpm, > 20 – 40 bpm, > 40 bpm
Pulse rate decrease from baseline	< 100 bpm; ≥ 100 bpm	≤ 20 bpm, > 20 – 40 bpm, > 40 bpm
SBP increase from baseline	< 140 mmHg; ≥ 140 mmHg	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
SBP decrease from baseline	< 140 mmHg; ≥ 140 mmHg,	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
DBP increase from baseline	< 90 mmHg; ≥ 90 mmHg	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
DBP decrease from baseline	< 90 mmHg; ≥ 90 mmHg,	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
Respiration rate increase from baseline	< 20 bpm; ≥ 20 bpm	≤ 5 bpm, > 5 – 10 bpm, > 10 bpm
Respiration rate decrease from baseline	< 20 bpm; ≥ 20 bpm	≤ 5 bpm, > 5 – 10 bpm, > 10 bpm

SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure.

For each participant, the worst post-baseline value (i.e., lowest and highest when applicable) will be calculated. For the definition of baseline values, see [section 9.2](#). Missing values will define a separate category.

The following summary will be prepared for vital sign parameters as grouped above:

- Maximal shifts from baseline (changes in categories)

A participant data listing will present data for all vital signs. Worst post-baseline values (highest and/or lowest values depending on vital sign), and changes from Baseline in the highest categories as defined in the table above will be identified.

15.5 ECG Evaluations

ECG summaries will include all ECG assessments collected at Baseline at start of DBPC and during the post-baseline period (DBPC Day 1 1-2 hours post dose, DBPC Week 4, DBPC Week 8, DBPC Week 16, DBPC Week 24 for the primary analysis, and including OLE Day 1 predose, OLE Day 1 1-2 hours post dose, OLE Week 4, OLE Week 12, OLE Week 24 as well for the secondary analysis). All ECG assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

The following analyses will be performed for each applicable ECG parameter (RR, PR, QRS, QT, ventricular rate -denoted as HR in what follows-, and QTcF) by cohort and study intervention group:

Descriptive statistics at Baseline, at each post-baseline time point and changes from baseline at each post-baseline time point by study intervention group, and in the following subgroups:

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

Frequency (number and percentage) of participants with notable ECG values according to the following categories by analysis visit:

- HR < 50 bpm, < 40 bpm, < 30 bpm
- HR increase from baseline > 20 bpm, > 30 bpm, > 40 bpm
- PR > 200 ms and > 220 ms
- PR increase from baseline > 30 ms
- QRS > 110 ms
- QTcF > 450 ms, > 480 ms, > 500 ms
- QTcF increase from baseline > 30 ms, > 60 ms

ECG interpretation (normal, abnormal/not clinically significant, abnormal/clinically significant) will be summarized at Baseline and during the on-treatment period.

A shift table from baseline to the worst post-baseline observation in ECG interpretation (normal, abnormal/not clinically significant, abnormal/clinically significant, missing and total) will also be provided.

Complete ECG profiles will be provided for participants with at least one notable ECG value or one notable ECG increase as defined above. For these participants, all ECG parameter values collected during the study will be provided. Listings of ECG absolute values and ECG interpretations will also be provided.

15.6 Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) assesses the suicidal behavior and suicidal ideation in participants. Abnormal findings identified via the C-SSRS will be recorded as AE.

Occurrence of suicidal behavior is defined as having answered “yes” to a least 1 of the 4 suicidal behavior subcategories (actual attempt, interrupted attempt, aborted attempt, preparatory acts or behavior).

Occurrence of suicidal ideation is defined as having answered “yes” to at least 1 of the suicidal ideation sub-categories (wish to be dead, non-specific 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).

Occurrence of suicidality is defined as having at least 1 occurrence of suicidal ideation or at least 1 occurrence of suicidal behavior.

The number and percentage of participants with occurrence of suicidal behavior, occurrence of suicidal ideation and occurrence of suicidality will be summarized by time point. Individual participant data listings will be also provided.

15.7 Spirometry and DLCO

An individual participant data listing of spirometry or DLCO will also be provided.

16 Analyses of Other Endpoints/Estimands

16.1 Pharmacokinetics

PK evaluation will be performed by the IQVIA Clinical PK/PD Group at final analysis.

Sparse blood PK samples will be collected for the assessment of enpatoran plasma concentration data in DM and PM participants during the DBPC and OLE period.

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All statistical analyses and descriptive summaries of PK data will be performed on the PKAS for the primary analysis after the DBPC and on the PKAS-OLE for the secondary analysis after the OLE Period.

Blood samples will be collected for enpatoran determination according to the following schedule:

Table 2: Pharmacokinetic Sampling Times for the DBPC Period

Study Day	Time (h)	Time from Scheduled Sampling Allowed
Day 1 and Day 29 (Week 4)	Predose	Within 60 minutes prior to dose administration
	1-2	Between 1 to 2 hours postdose on Day 1 and 29
	4-6	Between 4 to 6 hours postdose on Day 1 and 29
Day 57 (Week 8)	Predose	Within 60 minutes prior to dose administration
	1-2	Between 1 to 2 hours postdose on Day 57
Day 85 (Week 12)	Predose	Within 60 minutes prior to dose administration
Day 113 (Week 16)	Any time postdose	Any time post-morning dose
Day 141 (Week 20)		
Day 169 (Week 24/EOT)		

Table 3: Pharmacokinetic Sampling Times for the OLE Period

Study Day	Time (h)	Time from Scheduled Sampling Allowed
Day 1	Any time of the visit	Any time of the visit
Day 85 (Week 12)		
Day 169 (Week 24/EOT)		

16.1.1 Descriptive Statistics of PK Concentration Data

PK concentrations will be descriptively summarized by study period, study day, and time window (as appropriate) using: number of subjects included in the analysis set (N), number of non-missing observations (n), percent of non-missing observations (n %), arithmetic mean (Mean), SD, coefficient of variation (CV%, minimum (Min), median (Median), and maximum (Max). PK samples that are collected at any time postdose (Week 16, Week 20, and Week 24) will be summarized by study period and study day.

Descriptive statistics will only be calculated for $n > 2$ in which a measurement of below the lower limit of quantification represents a valid measurement and will be taken as zero for summary statistics of PK concentration data. In case $n \leq 2$, individual data will be presented (min, max) in summary tables. If the calculated mean or GeoMean is BLQ then it shall be reported in outputs as BLQ; SD, GeoCV% shall be reported as not determined (ND); LCI, UCI, Min, Median, and Max shall be reported as BLQ if applicable.

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data and rounded for reporting purposes only. PK concentrations will be carried over with full precision as provided in the source data without any rounding applied to CDISC SDTM PC and ADaM PC domains.

The following conventions will be applied when reporting descriptive statistics of PK concentration data:

n 0 decimal place

Mean, Min, Median, Max, 3 significant digits
SD:

CV%: 1 decimal place

16.1.2 Descriptive Statistics of PK Parameter Data

PK parameter data will be descriptively summarized using: number of non-missing observations, Mean, SD, coefficient of variation (CV%), Min, Median, Max, GeoMean, GeoCV% and the 95% CI for the GeoMean (LCI 95% GM, UCI 95% GM).

Descriptive statistics will only be calculated for a PK parameter when $n > 2$. In case $n \leq 2$, individual data will be presented (min, max) in summary tables.

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Descriptive statistics of PK parameter data will be calculated using full precision and rounded for reporting purposes only.

PK parameters will be provided with full precision, without any rounding applied to CDISC SDTM PP and ADaM PP domains.

The following conventions will be applied when reporting descriptive statistics of PK parameter data:

n	0 decimal place
Mean, Min, Median, Max, GeoMean, 95% CI, SD:	3 significant digits
CV%, GeoCV%:	1 decimal place

16.1.3 General Specifications for PK Concentration and PK Parameter Data

Predose samples that occur before the first drug administration will be assigned a time of 0 hours, as if the sample had been taken simultaneously with the study intervention administration. The same applies to the pre-dose sample of a multiple dose study.

Predose or trough samples which have been taken after the subsequent dosing will be reported as a protocol deviation. The resulting concentrations will be included in concentration listings but excluded from descriptive statistics of concentrations and from PK parameter estimation.

Values below the lower limit of quantification (BLQ) will be taken as zero for summary statistics of PK concentration data, CCI and for graphical presentations.

Missing concentrations (e.g. no sample, insufficient sample volume for analysis, no result or result not valid) will be reported and used generally as "N.R.". A participant who withdraws prior to the last planned observation will be included in the analyses up to the time of discontinuation.

If predose samples are collected outside of the hour prior to the morning dose administration, these will be excluded from the concentration summary and mean/median concentration plots. If

the subject misses the last dose before the PK blood collection, the sample should be collected and presented in listings but flagged and excluded from the statistical analysis. Postdose samples that are collected outside specified time windows will be excluded from concentration summaries and mean/median concentration plots.

PK concentrations which are erroneous due to a sampling processing or analytical error (as documented in the bioanalytical report) may be excluded from the PK analysis if agreed by the Sponsor. In this case the rationale for exclusion will be provided in the CSR. Any other PK concentrations that appear implausible to the Clinical Pharmacologist/Clinical PK/PD Scientist will not be excluded from the analysis. Any implausible data will be documented in the CSR.

If important protocol deviations occurred likely to affect the PK profile of participants as specified in [Section 10.2.1](#), the impacted concentrations and PK parameters will be excluded from summary statistics and further statistical evaluation.

Any PK concentrations or PK parameters excluded from summary statistics will be included in participants listings and flagged; a reason for exclusion will be detailed in the CSR (e.g. a footnote or a table of exclusions). Any flags should be included in the study specific CDISC data sets.

16.1.4 Estimation of Pharmacokinetic Parameters

The computer program Phoenix® WinNonlin® version 8.3, or higher (Certara, L.P., Princeton, New Jersey, USA) will be used to derive PK parameters applying non-compartmental analysis (NCA).

The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary NC, USA, windows version 9.1 or higher) may be used to generate additional PK parameters, or produce tables, listings, and figures.

16.1.4.1 Estimation of Pharmacokinetic Parameters in Plasma

In cases actual dosing time is missing, scheduled time might be used for NCA after performance of adequate plausibility checks and agreement with the sponsor. Decision and rationale should be included in the CSR. Otherwise, there will be no further imputation of missing data.

The following plasma PK parameters will be calculated where appropriate for the DBPC Period:

Symbol	Definition	Calculation
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Additional PK parameters may be calculated where appropriate.

Units for PK parameter output will be based on concentration and dose units used in the study, unless otherwise specified. In case concentration data units change within the study, PK parameters will be reported using consistent units throughout study outputs.

16.1.5 Presentation of PK Concentration and PK Parameter Data

16.1.5.1 Listings and Tables

The following PK tables will be produced (PKAS at DBPC and OLE Period):

- Descriptive statistics of concentrations by study period, study day, and time point/time interval, as appropriate. On study days where the PK sample collection is scheduled for any time during the visit; the summaries of concentration results will be grouped by time windows in ‘buckets’ such as 0 to < 2 h, 2 h to < 4 h, and 4 h to 6 h with final bucket windows to be assigned based on review of actual collection information.
- Descriptive statistics of PK parameters by study day for the primary analysis after DBPC

The following PK Listings will be produced (Safety Analysis Set at DBPC Period):

- Individual concentrations by participant, study day, and time point/time interval
- Individual PK parameters by participant and study day
- PK Sampling date and clock time, nominal time, actual time, time deviation, and concentration by participant sorted in chronological order
- Participants and/or data excluded from the PK analysis set, PK analysis, and/or descriptive statistics
- Phoenix WinNonlin NCA Core Output

The following PK Listings will be produced (Safety Analysis Set at OLE Period):

- Individual concentrations by participant, study day, and time point/time interval
- Individual PK parameters by participant and study day
- PK Sampling date and clock time, nominal time, actual time, time deviation, and concentration by participant sorted in chronological order
- Participants and/or data excluded from the PK analysis set, PK analysis, and/or descriptive statistics
- Phoenix WinNonlin NCA Core Output

16.1.5.2 Graphical Summaries and Individual plots (PK Analysis Set)

- CCI

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

[REDACTED]

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[REDACTED]

- [REDACTED]
- [REDACTED]

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16.3 Pharmacometric Analyses

Integrated Population PK, PK/PD and/or exposure-response modeling activities will be specified in a pharmacometrics analysis plan and results reported in a separate report.

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[REDACTED]

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17 References

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18 Appendices

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18.2 Appendix 2 – Corticosteroid Usage

18.2.1 General Rules

To perform derivations with regards to CS use at Baseline or during the on-treatment period, the following rules will be applied:

- CS will be medications collected in the “CORTICOSTEROID MEDICATION DETAILS” eCRF form.
- To derive oral CS use, only CS medications with route = oral will be considered. Prednisone-equivalent CS dose will be derived for oral use only.
- Concomitant CS medications are CS medications which are taken by participants any time during the on-treatment period, see [section 9.8](#).
- When dose per administration or dosing frequency is missing or uninterpretable, the corresponding CS will not be included in CS derivation but will be listed instead. An exception is when the start and stop dates occur the same day, no dosing frequency is applicable: these administrations will be included in calculations (daily dosing frequency will be assumed as equal to 1).

18.2.2 Missing Dates Handling

The following rules will apply to ensure the completion of start/end dates for all CS:

- For start date:
 - If the start date of the medication is unknown (i.e., completely missing date), the start date will be imputed with the date of 1st of January 2022 (one year before the year the trial started).
 - If both day and month are missing, but the year is available, the date will be imputed to the 1st of January.
 - If the day is missing only, it will be imputed to the first day of the month.

If the stop date is complete or partially missing, and the imputed start date is after the stop date then the start date will be imputed using the stop date.

- For end date:
 - If the end date of the CS is unknown (i.e., complete missing date and end relative to reference time point is not equal to ONGOING), the end date will be imputed to the 31st of December 2099.
 - If both day and month are missing, but the year is available, it will be imputed to the 31st of December.
 - If the day is missing only, it will be imputed to the last day of the month.

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

18.2.3 Conversions

The tables below provide conversions to be performed in order to assess the CS dosage:

Table 4: Conversion factors in prednisone equivalent

Who-drug Term	Conversion factor in prednisone equivalent
METHYLPREDNISOLONE	1,25
METHYLPREDNISOLONE SODIUM / METHYLPREDNISOLONE SODIUM SUCCINATE	1.25
METHYLPREDNISOLONE ACETATE	1.25
HYDROCORTISONE / HYDROCORTISONE SODIUM SUCCINATE	0.25
BETAMETHASONE	6.667
BETAMETHASONE DIPROPIONATE	6.667
BETAMETHASONE VALERATE	6.667
BETAMETHASONE PHOSPHATE	6.667
DEXAMETHASONE	6.667
TRIAMCINOLONE / TRIAMCINOLONE ACETONIDE	1.25
CORTISONE	0.2
PREDNISOLONE	1
PREDNISONE	1
DEFLAZACORT	0.83333
MEPREDNISONE	1,25
PARAMETHASONE	2,5
CRONOLEVEL	6.667
BETROSPAM	6.667

Table 5: Frequency conversions for CS

Frequency	Conversion factor	Numerical Conversion factor
OAM	1/30	0,0333
QOD	1/2	0,5000
QW	1/7	0,1429
QWK	1/7	0,1429
BID/Q12	2	2,0000
TID/Q8	3	3,0000
QD – including QD with AM or PM (e.g. QD[AM], QD[PM], QD at AM, QD at PM)	1	1,0000
ONCE	1	1,0000
QAM	1	1,0000
Q2H	12	12,0000
Q3H	8	8,0000
Q4H	6	6,0000
Q6H	4	4,0000
Q8H	3	3,0000
Q12H	2	2,0000
QHS	1	1,0000
QID/Q6	4	4,0000
QPM	1	1,0000
QH	24	24,0000
Q3W	1/21	0,0476
TIW or Three times a week	3/7	0,4286
Four times a week	4/7	0,5714
Q4W	1/28	0,0357
BIW or Twice a week	2/7	0,2857
EVERY 3 HOURS	8	8,0000
X1	1	1,0000
EVERY OTHER DAY	1/2	0,5000
EVERY OTHER DAY ALTERNATLY WITH 30 MG QOD	1/2	0,5000
EVERY OTHER DAY ALTERNATLY WITH 20 MG QOD	1/2	0,5000
ONCE A WEEK	1/7	0,1429
QD (EVERY MORNING)	1	1,0000
SINGLE DOSES	1	1,0000
ALTERNATE DAYS	1/2	0,5000

18.2.4 Corticosteroid usage, daily dose

Prednisone-equivalent daily dose (mg) by visit:

- Prednisone-equivalent CS daily dose is equal to the total dose (mg) the participant is receiving at the date of the scheduled visit (using conversion rules specified in [Section 18.2.3](#)). If several CS are taken at the same scheduled visit, then all CS doses should be added. If a prednisone-equivalent CS dose stopped/changed at the scheduled visit date (Week X visit date), then the prednisone-equivalent CS dose started before (Week X visit date - 1 day) will be considered as the CS daily dose for that visit.

CS dosing at Baseline is defined as CS dose taken the day of baseline visit (Day 1). If participant did not receive any CS at Baseline, then prednisone-equivalent CS dose is set to 0 mg.

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[REDACTED] [REDACTED]

[REDACTED] [REDACTED]

[REDACTED] [REDACTED]

[REDACTED] [REDACTED]

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

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

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

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- CCI [REDACTED]
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[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]

■ [REDACTED]

■ [REDACTED]

[REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

[REDACTED]

■ CCI [REDACTED]

■ [REDACTED]

■ [REDACTED]

[REDACTED] [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

[REDACTED] [REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

■ [REDACTED]

■ [REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

Signature Page for VV-CLIN-333832 v3.0

Approval Task	PPD [Redacted]
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Signature Page for VV-CLIN-333832 v3.0