Protocol Title:

A phase 2, randomized, double-blind, placebo-controlled, efficacy and safety study of daxdilimab subcutaneous injection in adult participants with inadequately controlled dermatomyositis or anti-synthetase inflammatory myositis

Protocol Number: HZNP-DAX-205 v2.0

Amendment Number: 2.0

Amendment Scope: Global

09 SEP 2024

Country/Region Identifier: ISO-3166

Compound: Daxdilimab

Brief Title:

A Phase 2 proof of concept study to evaluate the efficacy and safety of daxdilimab in participants with dermatomyositis or anti-synthetase inflammatory myositis

Study Phase: Phase 2

Sponsor Name: Horizon Therapeutics Ireland DAC

Legal Registered Address: 70 St Stephen's Green, Dublin 2, D02 E2X4, Ireland

Regulatory Agency Identifier Number: EU CT 2022-502810-10

SPONSORS SIGNATURE PAGE

Medical Representative		
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Biostatistics Representative		
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[redacted] PhD	Sr. Director, Biostatistics, Biometrics	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	09-Sep-2024
Amendment 1	27-Nov-2023
Original Protocol	27-Jul-2022

Amendment 2 (09-Sep-2024)

Overall Rationale for the Amendment:

This amendment incorporates feedback from regulatory agencies on hepatitis screening as part of study eligibility. Other changes focus on clarifications for permitted therapies, and enrollment feasibility challenges to reduce sample size to approximately 10 participants via protocol amendment with option for enrolled participants to continue dosing through 20 weeks. Participants who have received dosing beyond Week 20 will discontinue treatment and complete the procedures required at the EOT/ET visit 4 weeks after the last dose and then complete the SFU visits.

Original text including Section Number(s)	**Amended Text including Section Number(s)**	**Brief Rationale**
1.1 Synopsis Table 2 – Objectives and Endpoints, first bullet point Endpoint: [redacted]	1.1 Synopsis Table 2 – Objectives and Endpoints, first bullet point Endpoint: [redacted]	Updated study design due to recruitment and enrollment challenges.

Original text including Section Number(s)	**Amended Text including Section Number(s)**	**Brief Rationale**
1.1 Synopsis Table 2 – Objectives and Endpoints, first and second bullet points Endpoint	1.1 Synopsis Table 2 – Objectives and Endpoints, first and second bullet points Endpoint	Updated study design due to recruitment and enrollment challenges.
[redacted]		
1.1 Synopsis Table 2 – Objectives and Endpoints Endpoint	1.1 Synopsis Table 2 – Objectives and Endpoints Endpoint	Updated study design due to recruitment and enrollment challenges.
[redacted]		

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1.1 Synopsis Table 2 – Objectives and Endpoints Endpoint	1.1 Synopsis Table 2 – Objectives and Endpoints Endpoint	Updated study design due to recruitment and enrollment challenges.
[redacted]		
1.1 Synopsis Table 2 – Objectives and Endpoints Endpoint	1.1 Synopsis Table 2 – Objectives and Endpoints Endpoint	Updated study design due to recruitment and enrollment challenges.
[redacted]		

Original text including Section Number(s)	Amended Text including Section Number(s)	Brief Rationale
1.1 Synopsis Table 2 – Objectives and Endpoints Endpoint	1.1 Synopsis Table 2 – Objectives and Endpoints Endpoint	Updated study design due to recruitment and enrollment challenges.
[redacted]		
1.1 Synopsis 4.1 Overall Design Up to 96 participants will be randomized by population in a 1:1 ratio (24 participants per group) to receive investigational product (IP) (daxdilimab 300 mg or placebo) by subcutaneous (SC) injection once every 4 weeks (Q4W):	1.1 Synopsis 4.1 Overall Design Approximately 10 participants will be randomized by population in a 1:1 ratio. (2-3 participants per group) to receive investigational product (IP) (daxdilimab 300 mg or placebo) by subcutaneous (SC) injection once every 4 weeks (Q4W)	Updated study design due to recruitment and enrollment challenges.
1.1 Synopsis 4.1 Overall Design The estimated total study duration, from Screening to end of the Safety Follow-Up (SFU) period, will be up to 60 weeks, with visits to the clinic Q4W: 1. Screening period of approximately 4 weeks (Days -	1.1 Synopsis 4.1 Overall Design The estimated total study duration, from Screening to end of the Safety Follow-Up (SFU) period, will be up to approximately 36 weeks for participants in the randomized (first 24 weeks) portion of the study at amendment approval, and up to 60 weeks for	Updated study design due to recruitment and enrollment challenges.

Original text including Section Number(s)	Amended Text including Section Number(s)	Brief Rationale
28 to -1) 2. Treatment period from Day 1 through Week 48 - Randomization (double-blinded) on Day 1 - Administration of IP from Day 1 through Week 44 - Efficacy and safety assessments Q4W through Week 48 - Consisting of a randomized control period (RCP) and an open-label extension (OLE) period a. Randomized control period (double-blinded) from Day 1 through Week 24 Primary assessment of the efficacy endpoints will be done at Week 24, after which, participants in the placebo treatment groups (Groups 1 and 3) will be switched to receive 300 mg SC Q4W of daxdilimab for the duration of the study, and participants initially randomized to the daxdilimab 300 mg treatment groups (Groups 2 and 4) will continue to receive 300 mg SC Q4W of daxdilimab. b. Open-Label extension from Week 24 through Week 48 Although all participants will receive active treatment from Week 24, the blind for previous treatment (prior to Week 24) will	participants in the Open label extension. 1. Screening period of approximately 4 weeks (Days -28 to -1) 2. Treatment period from Day 1 through Week 24 - Randomization (double-blinded) on Day 1 - Administration of IP from Day 1 through Week 20 - Efficacy and safety assessments Q4W through Week 24 - Consisting of a randomized control period (RCP)(double-blinded) from Day 1 through Week 24 a. Randomized control period (double-blinded) from Day 1 through Week 24 Primary assessment of the efficacy endpoints will be done at Week 24. b. Open-Label extension from Week 24 through Week 48 No additional participants will enter the Open-label extension. Participants currently in the Open-label extension will stop dosing and perform the EOT /ET visit and safety follow-up visits. The schedule of activities for these visits are listed under the EOT/ET	

Original text including Section Number(s)	Amended Text including Section Number(s)	Brief Rationale
remain. 3. Safety Follow-Up period of 8 weeks, from Week 48 through Week 56 All administrations of IP will be administered by an unblinded pharmacist or nurse at the clinic and the participant will be observed for at least 60 minutes after the first and second doses and for 20 minutes for all subsequent doses. To maintain the blind for previous treatment, all participants will be observed for at least 60 minutes after the administration of IP at Weeks 24 and 28.	and Safety 1 and Safety 2 visits. Participants who have not yet entered the open-label extension will complete the Week 24 visit followed by safety follow up visits 3. Safety Follow-Up period of 8 weeks All administrations of IP will be administered by an unblinded pharmacist or nurse at the clinic and the participant will be observed for at least 60 minutes after the first and second doses and for 20 minutes for all subsequent doses.	
1.1 Synopsis 7.1 Discontinuation of IP In case of discontinuation of IP: · Participants who prematurely discontinue IP after Week 24 but remain in the study, will complete the End of Investigational Product Visit (Week 48) and the SFU period.	1.1 Synopsis 7.1 Discontinuation of IP In case of discontinuation of IP: · Participants who have received dosing beyond Week 20 will discontinue treatment and complete the procedures required at the EOT visit 4 weeks after the last dose and then complete the SFU visits.	Updated study design due to recruitment and enrollment challenges.
7.1 Discontinuation of IP It may be necessary for a participant to permanently discontinue IP. Discontinuation of IP does not represent	7.1 Discontinuation of IP The IP must be permanently discontinued if the Investigator determines that continuing it would result in a significant safety	Feedback from Regulatory Agency

Original text including Section Number(s)	Amended Text including Section Number(s)	Brief Rationale
withdrawal from the study. The primary reason for discontinuation from IP should be recorded in the eCRF using one of the following categories • Lack of Efficacy • AE – the participant experiences an AE that imposes an unacceptable risk to the participant's health (eg, anaphylactic reaction), or the participant is unwilling to continue therapy because of an AE; a Common Terminology for Adverse Events (CTCAE) Grade 3 or higher allergic reaction or infection considered to be related to the trial intervention (see Section 10.2.3); or another AE that contraindicates further dosing in the opinion of the Investigator and/or the Sponsor, or medical monitor. Participants who discontinue treatment due to an AE should be followed until resolution or stabilization of the AE, or an adequate explanation for the event is obtained; • Physician decision – the investigator has determined that the administration of IP poses an unacceptable	risk for that participant and for the additional reasons described below. • Withdrawal of consent for continued study participation • Withdrawal of consent for further treatment with IP • Receipt of prohibited medications that require discontinuation of IP • Pregnancy, lactation, or a decision to become pregnant • Any SAE that is considered to be related to IP by the Investigator, the Sponsor, or the SDMC • Any of liver safety related events (Section 10.4) • Anaphylaxis or a CTCAE Grade 4 hypersensitivity reaction that is considered to be related to IP the Investigator, the Sponsor, or the SDMC • Any CTCAE grade 3 opportunistic infection (see Section 10.6, Appendix 3) that is considered to be related to IP the Investigator, the Sponsor, or the SDMC • Hematologic Malignancy • An AE that, in the opinion of the Investigator, the SDMC, and/or the Sponsor,	

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risk to the participant (specify reason); • Participant decision (specify reason); • Lost to Follow-up – the participant does not return to the clinic for scheduled assessments, and does not respond to the site's attempts to contact the participant; • Receipt of prohibited therapy (Section 6.9.2). • Study Terminated by Sponsor – the Sponsor, Institutional Review Board (IRB), or regulatory agency terminates the study; • Pregnancy or decision to become pregnant.	warrants discontinuation of further dosing. • Any other reason when the Investigator determines that continuing IP would result in a significant safety risk for that participant.	
1.1 Synopsis In case of withdrawal of consent or lost to follow-up: · Participants who withdraw should perform an End of Study/Early Termination Visit (Week 56), as shown in the SOA (section 1.3) if consent for this visit is not also withdrawn. If a participant withdraws consent to participate in the study, then no further study visits or data collection should take place.	1.1 Synopsis In case of withdrawal, withdrawal of consent or lost to follow-up: · Participants who withdraw should perform an End of Study/Early Termination Visit if consent for this visit is not also withdrawn. If a participant withdraws consent to participate in the study, then no further study visits or data collection should take place.	Updated study design due to recruitment and enrollment challenges.

Original text including Section Number(s)	Amended Text including Section Number(s)	Brief Rationale
1.1 - Synopsis 5.1 - Inclusion Criteria #4 4. A diagnosis of definite or probable myositis according to ACR/EULAR 2017 criteria (A OR B): - A. Total aggregated score ≥ 5.5 without a [redacted] Note: Pathognomonic skin rash (such as heliotrope rash, Gottron's papules and/or Gottron's sign) is required if no [redacted] is available	1.1 Synopsis 5.1 Inclusion Criteria #4 4. A diagnosis of definite or probable myositis according to ACR/EULAR 2017 criteria (A OR B): - A. Total aggregated score ≥ 5.5 without a [redacted] Note: Pathognomonic skin rash (such as mechanic's hands, heliotrope rash, Gottron's papules and/or Gottron's sign) is required if no [redacted] is available	Clarification to add mechanic's hands as a pathognomonic skin rash.
1.1 Synopsis 5.2 Exclusion Criteria #8 8. Major surgery within 8 weeks prior to Screening or elective surgery planned from Screening through Week 48.	1.1 Synopsis 5.2 Exclusion Criteria #8 8. Major surgery within 8 weeks prior to Screening or elective surgery planned from Screening through end of the study.	Updated study design due to recruitment and enrollment challenges.
1.1 Synopsis 5.2 Exclusion Criteria #11 11. History of cancer within the past 5 years.	1.1 Synopsis 5.2 Exclusion Criteria #11 11. History of cancer within the past 5 years, except cutaneous basal cell or squamous cell carcinoma treated with curative therapy.	Feedback from Regulatory Agency and Investigators
1.1 Synopsis	1.1 Synopsis	Feedback from Regulatory Agency

Original text including Section Number(s)	Amended Text including Section Number(s)	Brief Rationale
5.2 Exclusion Criteria #17 17. All participants will undergo testing for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) during Screening. - Participants who are HBsAg positive are not eligible for the study. - Participants who are HBsAg negative and HBcAb positive will be reflex tested for hepatitis B surface antibody (HBsAb). If HBsAb is positive, may be enrolled in the study; if HBsAb is negative, the participant is not eligible for the study.	5.2 Exclusion Criteria #17 17. All participants will undergo testing for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) during Screening. - Participants who are HBsAg positive are not eligible for the study. - Participants who are HBsAg negative and HBcAb positive will be reflex tested both for hepatitis B surface antibody (HBsAb) and hepatitis B virus (HBV) DNA. If HBsAb is positive and HBV DNA is negative, may be enrolled in the study; if HBsAb is negative or HBV DNA is positive, the participant is not eligible for the study.	
1.1 Synopsis 9.5 Sample Size Determination Sample Size Determination: [redacted]	1.1 Synopsis 9.5 Sample Size Determination Sample Size Determination: [redacted]	Updated study design due to recruitment and enrollment challenges.

Original text including Section Number(s)	Amended Text including Section Number(s)	Brief Rationale
[redacted]		
1.1 Synopsis 9.3.2 Primary Endpoint Efficacy Analysis 9.3.3 Secondary Endpoint Efficacy Analysis Statistical Analysis Methods: · Primary efficacy endpoint: Within each of the DM and ASIM populations, the primary efficacy endpoint of TIS at Week 24 will be analyzed using a mixed model for repeated measures (MMRM), with treatment, visit, visit by treatment interaction, and randomization stratification factor included in the model. · Secondary efficacy endpoint: Within each of the DM and ASIM populations, the binary and continuous secondary endpoints will be analyzed using a logistic regression model with treatment, baseline oral corticosteroid (OCS) dose (OCS reduction endpoint only), and	1.1 Synopsis 9.3.2 Primary Endpoint Efficacy Analysis 9.3.3 Secondary Endpoint Efficacy Analysis Statistical Analysis Methods: · Primary efficacy endpoint: Within each of the DM and ASIM populations, the primary efficacy endpoint of TIS at Week 24 will be summarized descriptively based on the observed data using Full Analysis Set. · Secondary efficacy endpoint: Within each of the DM and ASIM populations, the binary and continuous secondary endpoints will be summarized descriptively based on the observed data using Full Analysis Set.	Updated study design due to recruitment and enrollment challenges.

Original text including Section Number(s)	Amended Text including Section Number(s)	Brief Rationale
randomization stratification factor included in the model. Within each of the DM and ASIM populations, the change from Baseline to Week 24 in CDASI activity score will be analyzed using a MMRM approach, with treatment, visit, visit by treatment interaction, randomization stratification factor and baseline CDASI activity score included in the model. The missing data are handled by the MMRM approach.		
1.1 Synopsis 9.4.1 Interim Analysis 9.4.2 Primary Analysis Interim analysis: An interim analysis will be conducted after 50% of the participants from the DM population have completed Week 24 visit. The efficacy and safety data collected prior to the data cut-off for the interim analysis will be analyzed for each of the DM and ASIM populations. No multiplicity adjustment is planned, because the study will not be stopped early at this interim analysis to claim efficacy. The details of the interim analysis will be specified in an interim unblinding analysis plan prior to unblinding. Primary analysis: The primary analysis will be conducted separately for each of the DM and ASIM populations after the	1.1 Synopsis Interim analysis: This is not to be conducted thus not applicable. Original sections 9.4.1 (interim analysis) and 9.4.2 (primary analysis) removed. Section 9.4.1 replaced with title of Final Analysis. Primary analysis: The primary analysis will be conducted separately for each of the DM and ASIM populations after the last participant has completed the Week 24 visit or discontinued from study prior to Week 24 for that population. For the primary analysis, all the efficacy and safety data collected prior to the data cut-off will be analyzed.	Updated study design due to recruitment and enrollment challenges.

Original text including Section Number(s)	Amended Text including Section Number(s)	Brief Rationale
last participant has completed the Week 24 visit or discontinued from study prior to Week 24 for that population. For the primary analysis, all the efficacy and safety data collected prior to the data cut-off will be analyzed.		
2.3.1 Risk Assessment – beginning fifth paragraph In Study VIB7734.P2.S1, a Phase 2, double-blind, placebo-controlled efficacy and safety study, once every 4 weeks (Q4W) or once every 12 Weeks 200 mg SC doses of daxdilimab, with an additional 200 mg SC dose at Week 4, or placebo are planned to be administered to 194 adult participants with moderate to severely SLE. Up to 17 May 2022, there have been 2 suspected unexpected serious adverse reactions (SUSARs) described as infections (pneumonia and herpes zoster). Important potential risks for daxdilimab include viral infection and viral reactivation, opportunistic infection, malignancy (other than non-melanoma skin cancer), and hypersensitivity reactions including anaphylaxis. Other potential risks include vaccine interaction, drug-drug interactions, and reproductive toxicity.	2.3.1 Risk Assessment – beginning fifth paragraph Study VIB7734.P2.S1 was a randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the safety and efficacy of daxdilimab in adults with moderate to severely active SLE. The study enrolled 214 participants into 3 groups. Participants received placebo, daxdilimab 200 mg Q4W, or daxdilimab 200 mg every 12 weeks (Q12W) by SC injection. During the study, 107 of 143 (74.8%) daxdilimab-treated participants and 49 of 71 (69.0%) placebo-treated participants experienced at least one TEAE. There was one death in the study, which was not considered to be related to the IP by the Investigator. One SAE (Grade 2 pneumonia), reported in a participant in the daxdilimab 200 mg Q4W group, was considered to be related to IP by the Investigator. One additional SAE (Grade 3 herpes zoster), reported in a participant in the daxdilimab 200 mg Q4W group, was considered related to IP by the Sponsor. Eight	Updated study design due to recruitment and enrollment challenges.

Original text including Section Number(s)	Amended Text including Section Number(s)	Brief Rationale
A detailed description of the chemistry, pharmacology, efficacy, and safety of daxdilimab is provided in the current version of the IB.	daxdilimab-treated participants and one placebo-treated participant experienced events leading to treatment discontinuation. Across all treatment groups, TEAEs were most frequently reported in the system organ class of Infections and infestations (52.4% of daxdilimab-treated participants and 46.5% of placebo-treated participants). For the daxdilimab-treated participants, the most frequently reported TEAEs by preferred term were COVID-19 (13.3%) and urinary tract infection (10.5%); the majority of the TEAEs by preferred term were only reported in 1 (0.7%) or 2 (1.4%) participants. No relationship was observed in the frequency of TEAEs for the 2 dose frequencies studied. Study HZNP-DAX-201 is an open-label, proof-of-concept trial to assess the preliminary efficacy, safety, tolerability, PK, and PD of daxdilimab in participants with moderate to severe alopecia areata. The study enrolled 30 participants who received daxdilimab 300 mg Q4W by SC injection for 32 weeks (9 doses). As of the Week 24 primary analysis (data cut-off date 08 Sep 2023), 14 participants had completed the treatment period and 9 participants had completed the trial. As of 08 Sep 2023, 21 of the 30 (70.0%) daxdilimab-treated participants experienced at least one TEAE. There were no deaths,	

Original text including Section Number(s)	Amended Text including Section Number(s)	Brief Rationale
	no TESAEs, and no AEs leading to treatment discontinuation. Treatment-emergent AEs were most frequently reported in the system organ class of Infections and infestations (46.7%) and General disorders and administration site conditions (30.0%). The most frequently reported TEAEs by preferred term were injection site reaction (20.0%) and nasopharyngitis (16.7%); all other TEAEs by preferred term were reported in 1 (3.3%) or 2 (6.7%) participants. To date, injection site reactions have been determined to be a non-important identified risk for daxdilimab. Important potential risks for daxdilimab include viral infection and viral reactivation, opportunistic infection, malignancy (other than non-melanoma skin cancer), and hypersensitivity reactions including anaphylaxis. Other potential risks include vaccine interaction, drug-drug interactions, and reproductive toxicity. A detailed description of the chemistry, pharmacology, efficacy, and safety of daxdilimab is provided in the current version of the IB.	
1.3 Schedule of Activities – prior Table 1	1.3 Schedule of Activities – current Table 1 Table 1 has been modified significantly from the previous	Updated study design due to recruitment and enrollment challenges.

<table>
<tr><th>Original text including Section Number(s)</th><th>Amended Text including Section Number(s)</th><th>Brief Rationale</th></tr>
<tr><td>Table 1 from Amendment 1 has been modified significantly due to the updated study design.</td><td>version Table 1 and is included as Appendix 7 within protocol version 2.0.</td><td></td></tr>
<tr><td>4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure (Week 56) shown in the SoA (Section 1.3) for the last participant in the study globally.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit or the last scheduled procedure (week 56) shown in the SOA</td><td>4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the study globally.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the study globally.</td><td>Updated study design due to recruitment and enrollment challenges.</td></tr>
<tr><td>6.7 Continued Access to IP after the End of the Study.

A long-term extension (LTE) study for safety and efficacy may be offered as part of a separate or an amended protocol to participants who complete the Week 48 visit. Participants who enter the LTE study directly after completion of the Week 48 visit will not complete the visits of the SFU period.</td><td>6.7 Continued Access to IP after the End of the Study.

The sponsor will not continue provision of investigational product for subjects after their study participation ends unless it is a legal requirement.</td><td>Clarification</td></tr>
<tr><td>Table 4 – Dose Groups
<table><tr><th>Dose up to Week 24</th><th>Dose Weeks 24 to 44</th></tr><tr><td>0 mg (no drug)</td><td>300 mg</td></tr></table></td><td>Table 4 – Dose Groups
<table><tr><th>Dose up to Week 20</th><th><s>Dose Weeks 24 to 44</s></th></tr><tr><td>0 mg (no drug)</td><td><s>300 mg</s></td></tr></table></td><td>Updated study design due to recruitment and enrollment challenges.</td></tr>
</table>

Original text including Section Number(s)	Amended Text including Section Number(s)	Brief Rationale
300 mg / 300 mg 0 mg (no drug) / 300 mg 300 mg / 300 mg	300 mg / ~~300 mg~~ 0 mg (no drug) / ~~300 mg~~ 300 mg / ~~300 mg~~	
Table 5 – Permitted Standard of Care Medication Drug: Hydroxychloroquine Washout period prior to first dose: 8 weeks Maximally allowed stable dose: 0.2mg/kg	Table 5 – Permitted Standard of Care Medication Drug: Hydroxychloroquine Washout period prior to first dose: 8 weeks Maximally allowed stable dose: 400mg daily	Updated to align with standard of practice
8.2.4 Steroid Taper – text found after Table 7 For participants who remain stable or improving during OLE, investigators should continue to taper participants off corticosteroids (prednisone or equivalent) as clinically tolerated. Recommended taper is 2.5mg/day every 4 weeks until 5mg/day, then 1mg/day every 2 weeks until discontinued	8.2.4 Steroid Taper – text found after Table 7 ~~For participants who remain stable or improving during OLE, investigators should continue to taper participants off corticosteroids (prednisone or equivalent) as clinically tolerated. Recommended taper is 2.5mg/day every 4 weeks until 5mg/day, then 1mg/day every 2 weeks until discontinued~~ Table 8 – Recommended Steroid Taper During OLE was removed If symptoms worsen, participants should call the investigator for instructions (eg, hold at current dose or step back up to previous dose).	Updated study design due to recruitment and enrollment challenges. Table 8 (Recommended Steroid Taper During OLE) removed due to not being applicable with updated study design.

Original text including Section Number(s)	Amended Text including Section Number(s)	Brief Rationale
8.3.5 Pregnancy Testing A urine pregnancy test will be performed by study staff at the clinic and prior to the administration of IP from Day 1 through Week 24, 48 and at the End of Study visit (Week 56)	8.3.5 Pregnancy Testing A urine pregnancy test will be performed by study staff at the clinic and prior to the administration of IP from Day 1 through Week 24 and at the End of Study visit	Updated study design due to recruitment and enrollment challenges.
8.3.6 Local Injection Tolerability Assessments Local injection tolerability assessments will be performed approximately 30 minutes postdose (can be performed any time at Week 48 as no IP is administered) at the visits specified in the SOA. The investigator, or designee, will evaluate the injection sites at these visits, document the presence or absence of local intolerance/injection site reactions, and will open an AE in case of local injection site intolerance. Additional follow-up after Week 48 can be performed for any ongoing injection site reactions.	8.3.6 Local Injection Tolerability Assessments Local injection tolerability assessments will be performed approximately 30 minutes postdose (can be performed any time at non-dosing visits) The investigator, or designee, will evaluate the injection sites at these visits, document the presence or absence of local intolerance/injection site reactions, and will open an AE in case of local injection site intolerance. Additional follow-up after the last treatment visit can be performed for any ongoing injection site reactions.	Updated study design due to recruitment and enrollment challenges.
10.1.6 Data Protection - Information added on Serious Breach	10.1.6 - Data Protection - additional text added to section: Serious Breach Suspected Serious Breaches must be reported to the study team or the Clinical Out-of-Hours Support Program:	Added new information to clarify serious breach

Original text including Section Number(s)	Amended Text including Section Number(s)	Brief Rationale
	https://wwwext.amgen.com/science/clinical-trials/clinical-out-of-hours- A Serious Breach is a breach of any of the following: · Good Clinical Practice (GCP) · the clinical trial protocol · an applicable regulation that is likely to impact to a significant degree either of the following: · the safety, physical, or mental integrity and the rights of the subject · the reliability and robustness of the data and the scientific value of the trial	
10.2.2 Definition of SAE Last bullet point of section: Is a suspected transmission of any infectious agent via an authorized medicinal product	10.2.2 Definition of SAE Bullet point removed: ~~Is a suspected transmission of any infectious agent via an authorized medicinal product~~	Correction
10.1.8 **Dissemination of Clinical Study Data** Study results will be published on ClinicalTrials.Gov within 1 year of end of study. Additionally, information may be found at clinicaltrialsregister.eu/.	10.1.8 **Dissemination of Clinical Study Data** Study results will be published on ClinicalTrials.Gov and Clinical Trials Information System (CTIS) within 1 year of end of study. Additionally, information may be found at clinicaltrialsregister.eu/.	Update to include new EU CTR CTIS reporting requirements
10.2.4. Reporting of SAEs –	10.2.4. Reporting of SAEs –	Clarification

Original text including Section Number(s)	**Amended Text including Section Number(s)**	**Brief Rationale**
Review each SAE report and evaluate the relationship of the SAE to study drugs.	Review each SAE report and evaluate the relationship of the SAE to study drugs. a. If not related to study drug but related to a study procedure or study activity, this should be noted within the SAE narrative.	
10.2.4. Reporting of SAEs – Reporting of IND Safety Reports The sponsor will notify the regulatory agencies and all investigators on any new serious risks associated with the drug and comply with country-specific regulatory requirements relating to safety reporting.	10.2.4 Reporting of SAEs – Reporting of Expedited Safety Information The sponsor will notify the regulatory agencies and all investigators on any new serious risks associated with the drug and comply with country-specific regulatory requirements relating to safety reporting.	Correction to header of section.
6.1 Study Interventions Administered – third paragraph Both IPs are to be administered by SC injection Q4W from Day 1 to Week 24. After Week 24 through Week 44, only daxdilimab will be administered to wants. To maintain the same number and volume of injections across all groups, the required dose will be administered as 2 injections of 1.5 mL.	6.1 Study Interventions Administered – third paragraph Both IPs are to be administered by SC injection Q4W from Day 1 to Week 20. To maintain the same number and volume of injections across all groups, the required dose will be administered as 2 injections of 1.5 mL.	Updated study design due to recruitment and enrollment challenges.
6.4 Blinding (sub bullet) Although all participants will receive active treatment from Week 24, the blind for previous	6.4 Blinding (sub bullet) Although all participants who have received dosing past the Week 20 visit will received active treatment from Week 24, the blind for	Clarification

Original text including Section Number(s)	**Amended Text including Section Number(s)**	**Brief Rationale**
treatment (prior to Week 24) will remain.	previous treatment (prior to Week 24) will remain in force until appropriate data analysis is completed.	
Throughout protocol	Throughout protocol, mentions of Weeks 36, 40, 44, and 48 were removed and replaced with study visits consistent with the new protocol.	Updated study design due to recruitment and enrollment challenges.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR/EULAR 2017	American College of Rheumatology/European League Against Rheumatism 2017
ADA	antidrug antibodies
AE	adverse event
AESI	adverse event of special interest
ASIM	anti-synthetase inflammatory myositis
CDASI	cutaneous dermatomyositis disease area and severity index
CFR	Code of Federal Regulations
CLE	cutaneous lupus erythematosus
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CSM	core set measures
CSR	Clinical Study Report
CTCAE	common terminology for adverse events
DILI	drug-induced liver injury
DM	dermatomyositis
ECG	electrocardiogram
eCRF	electronic case report form
EOT	End of Treatment
ET	Early Termination
FI	functional index
FSH	follicle-stimulating hormone
[redacted]	
GCP	Good Clinical Practices
HAQ-DI	health assessment questionnaire-disability index
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy

Abbreviation	Definition
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
Ig	immunoglobulin
IGRA	IFNγ release assay
IHC	immunohistochemistry
ILT7	immunoglobulin-like transcript 7
IP	investigational product
IRB	Institutional Review Board
IVIG	intravenous immunoglobulin
IVRS/IWRS	interactive voice/web response system
LAR	legally authorized representative
LTE	long-term extension
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	
MDI	myositis damage index
MMT	manual muscle testing
MMRM	mixed model for repeated measures
[redacted]	
OCS	oral corticosteroid
OLE	open-label extension
[redacted]	
pDC	plasmacytoid dendritic cell
PEF	peak expiratory function
[redacted]	
PhGDA	physician global disease activity
PK	pharmacokinetics
PM	polymyositis
[redacted]	

Abbreviation	Definition
PtGDA	patient global disease activity
Q4W	once every 4 weeks
RCP	randomized control period
REB	Research Ethics Board
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SARS-CoV-2	severe acute respiratory syndrome-coronavirus-2
SDMC	Safety Data Monitoring Committee
SFU	Safety Follow-Up
SLE	systemic lupus erythematosus
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent SAE
TIS	total improvement score
ULN	upper limit of normal
VAS	visual analog scale
WOCBP	women of childbearing potential
WONCBP	woman of nonchildbearing potential

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Phase 2, randomized, double-blind, placebo-controlled, efficacy and safety study of daxdilimab subcutaneous injection in adult participants with inadequately controlled dermatomyositis or anti-synthetase inflammatory myositis.

Brief Title:

A Phase 2 proof of concept study to evaluate the efficacy and safety of daxdilimab in participants with dermatomyositis or anti-synthetase inflammatory myositis.

Regulatory Agency Identifier Number(s):

Registry	ID
EU CT	2022-502810-10

Rationale:

Idiopathic inflammatory myopathies, including dermatomyositis (DM) and anti-synthetase inflammatory myositis (ASIM), can result in permanent muscle damage with weakness if not controlled promptly. Currently, corticosteroids, intravenous immunoglobulin (IVIG), and other immune modulators are used for treatment, but these medications are also associated with noticeable side effects including risk for diabetes, osteoporosis, cataracts, opportunistic infections, and thrombosis. In addition, some patients do not achieve timely control of their disease with these therapies. This, together with the burden of their side effects, yields the clinical need for a therapy to treat these patients.

Daxdilimab is being developed for the treatment of multiple autoimmune disorders in which plasmacytoid dendritic cells (pDCs) are believed to contribute to the pathogenesis, including DM and ASIM. The inflammatory response in these disorders is characterized by the production of large amounts of type I interferons by pDCs. Daxdilimab has the capacity to specifically bind to the surface of pDCs, induce apoptosis, and deplete pDCs in vivo. It is hypothesized that the depletion of pDCs induced by daxdilimab will reduce disease activity in patients with DM or ASIM.

Phase 1 clinical studies have tested the safety, tolerability, pharmacokinetics (PK), [redacted] and immunogenicity of different doses of daxdilimab in participants with autoimmune disorders, such as DM, polymyositis (PM), Sjogren's syndrome, systemic lupus erythematosus (SLE), cutaneous lupus erythematosus (CLE) or systemic sclerosis. Additionally, Phase 2 studies are being performed or planned to test the safety and efficacy of daxdilimab in treating moderate to severely active SLE, alopecia areata, and discoid lupus erythematosus, which yields the need for a similar study in participants with DM or ASIM.

Objectives and Endpoints:

Objectives	Endpoints
Primary Efficacy	
• To evaluate the effect of daxdilimab compared with placebo in reducing disease activity at Week 24.	• TIS at Week 24.
Secondary Efficacy	
• To evaluate the effect of daxdilimab compared with placebo in reducing disease activity at Week 24.	• Proportion of participants with improvement of TIS ≥ 40 and without deterioration at 2 consecutive visits at 24 weeks. • Proportion of participants with improvement of TIS ≥ 20 and without deterioration at 2 consecutive visits at 24 weeks.
• To evaluate the effect of daxdilimab compared with placebo on skin symptoms at Week 24.	• Change in the CDASI activity score from Baseline (Day 1) to Week 24.
• To evaluate the effect of daxdilimab on decreasing the use of corticosteroid at Week 24.	• Proportion of participants on an OCS dose ≥ 10 mg of prednisone or equivalent at Baseline who achieve a clinically meaningful reduction in the OCS dose: either a 25% decrease or an OCS dose of 7.5 mg/day of prednisone or equivalent at Week 24.
Pharmacokinetics and Immunogenicity	
• To characterize the PK and immunogenicity of daxdilimab in participants.	• Serum concentration of daxdilimab over time. • Prevalence at Baseline and incidence and titer of ADA directed against daxdilimab over time.
Safety	
• To evaluate the safety and tolerability of daxdilimab in participants.	• Incidence of TEAEs • Incidence of TESAEs • Incidence of TEAESIs: hypersensitivity reaction, including anaphylaxis, herpes zoster infection, severe (CTCAE Grade 3 or higher) viral infection/reactivation, opportunistic infection, and malignancy (except non-melanoma skin cancer).

Objectives	Endpoints
Exploratory	
[redacted]	

Objectives	Endpoints
[redacted]	

ADA = antidrug antibodies; CDASI = cutaneous dermatomyositis disease area and severity index; CSM = core set measures; CTCAE = common terminology for adverse events; [redacted] pDCs = plasmacytoid dendritic cells; [redacted]; PK = pharmacokinetics; [redacted] TEAEs = treatment-emergent adverse events; TESAEs = treatment-emergent serious adverse events; TEAESIs = treatment-emergent adverse events of special interest; TIS = total improvement score

Overall Design and Brief Summary:

This study is a Phase 2, randomized, double-blind, placebo-controlled, proof of concept study to assess the efficacy and safety of daxdilimab in participants aged ≥ 18 to ≤ 75 years with DM or ASIM.

All participants will read and sign an informed consent form (ICF) prior to any study procedures being performed. Participants who meet all inclusion criteria and none of the exclusion criteria may be accepted into the study.

The study will enroll 2 idiopathic inflammatory myositis participant populations:

- Population 1 or DM: participants with DM with definite or probable myositis according to the American College of Rheumatology/European League Against Rheumatism 2017 (ACR/EULAR 2017) criteria and a DM rash.
- Population 2 or ASIM: participants with ASIM with definite or probable myositis according to ACR/EULAR 2017 criteria and a positive ASIM associated antibody.

Approximately 10 participants will be randomized by population in a 1:1 ratio (2-3 participants per group) to receive investigational product (IP) (daxdilimab 300 mg or placebo) by subcutaneous (SC) injection once every 4 weeks (Q4W):

- Group 1: DM placebo
- Group 2: DM daxdilimab 300 mg
- Group 3: ASIM placebo

- Group 4: ASIM daxdilimab 300 mg

Randomization will take place, at the latest, 28 days after successful screening and it will be stratified by Manual Muscle Testing 8 (MMT8) score (≤ 120 vs > 120) at Baseline (Day 1).

The estimated total study duration, from Screening to the end of the Safety Follow-Up (SFU) period, will be up to approximately 36 weeks for participants in the randomized (first 24 weeks) portion of the study at amendment approval, and up to 60 weeks for participants in the Open-label extension.

1. Screening period of approximately 4 weeks (Days -28 to -1)
2. Treatment period from Day 1 through Week 24
   - Randomization (double-blinded) on Day 1
   - Administration of IP from Day 1 through Week 20
   - Efficacy and safety assessments Q4W through Week 24
   - Consisting of a randomized control period (RCP) (double-blinded) from Day 1 through Week 24:
     a. Randomized control period (double-blinded) from Day 1 through Week 24

        Primary assessment of the efficacy endpoints will be done at Week 24.

     b. Open-Label extension from Week 24 through Week 48

        No additional participants will enter the Open-label extension. Participants currently in the Open-label extension will stop dosing and perform the EOT/ET visit and safety follow-up visits. The schedule of activities for these visits are listed under the EOT/ET visit and Safety 1 and Safety 2 visits.

        Participants who have not yet entered the open-label extension will complete the Week 24 visit followed by safety follow up visits.

        Participants who have received dosing beyond Week 20 will discontinue treatment and complete the procedures required at the EOT visit 4 weeks after the last dose and then complete the SFU visits.

3. Safety Follow-Up period of 8 weeks

All administrations of IP will be done by an unblinded pharmacist or nurse at the clinic and the participant will be observed for at least 60 minutes after the first and second doses and for 20 minutes for all subsequent doses.

The primary efficacy objective is to demonstrate that daxdilimab is superior to placebo in reducing disease activity at Week 24. To do so, the following assessments will be performed:

- Total improvement score (TIS) based on the 6 core set measures (CSM):
  [redacted]
  3. Physician global disease activity (PhGDA) (part of the [redacted]

4. MMT8 bilateral
5. Laboratory muscle enzymes
6. Extramuscular global assessment (part of the [redacted]

- [redacted]
- Cutaneous dermatomyositis disease area and severity index (CDASI)
- Steroid taper
- [redacted]

The safety of daxdilimab will be assessed by:

- Measurement of physical examinations
- Monitoring of vital signs
- Electrocardiograms (ECGs)
- Monitoring of hematology, blood chemistry, and urinalysis
- Pregnancy testing
- Assessment of local injection tolerability
- Monitoring and recording of all adverse events

The quality of life of the participants will be assessed with:

- [redacted]

To characterize the PK, [redacted] and immunogenicity of daxdilimab, blood samples from all participants, and optional [redacted] from those who agree, will be collected.

Unless otherwise specified, the study assessments scheduled on Day 1 must be performed before the administration of IP. Patient-reported outcomes will be performed first, followed by the physician assessments, measurement of vital signs, and laboratory assessments.

In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

In case of discontinuation of IP:

- Participants who prematurely discontinue IP prior to Week 24 will be followed according to the regularly scheduled evaluations until Week 24 and at least 12 weeks after the last administration of IP, whichever is longer, unless they withdraw consent from study participation or are lost to follow-up.
- Participants who have progressed past Week 20 will discontinue treatment and complete the end of treatment visit 4 weeks after their last dose followed by 8 weeks of safety follow-up.

In case of withdrawal of consent or lost to follow-up:

- Participants who withdraw should perform an End of Study/Early Termination Visit as shown in the SoA (Section 1.3), if consent for this visit is not also withdrawn. If a participant withdraws consent to participate in the study, then no further study visits or data collection should take place.
- Before a participant is deemed lost to follow-up, the investigator must make every effort to reach the participant by phone, e-mail, or certified letter and document these attempts in the participant's medical record. Should the participant continue to be unreachable, the participant will be considered lost to follow-up.

To minimize bias:

- For the first 24 weeks, the study will be double-blind, which means that participants, investigators, and the study personnel will be unaware of the IP given to the participant.
- From Week 24, the study will be open-label, but the blinding for previous treatment (prior to Week 24) will remain.
- An uninvolved, unblinded pharmacist/IP Manager or study-site staff member will be responsible for the dispensation and administration of all IPs and will endeavor to ensure that there are no differences in time taken to dispense following Randomization.

The study will be conducted on an outpatient basis globally.

Inclusion Criteria:

Informed Consent

1. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the United States) obtained from the participant/legal representative prior to performing any protocol-related procedures, including screening evaluations.
2. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the study.

Age and Sex

3. Adult men or women ≥ 18 and ≤ 75 years of age at the time of signing the ICF.

Type of Participant and Disease Characteristics

4. A diagnosis of definite or probable myositis according to ACR/EULAR 2017 criteria (A OR B):
   - A. Total aggregated score ≥ 5.5 without a [redacted]

     Note: Pathognomonic skin rash (such as mechanic's hands, heliotrope rash, Gottron's papules and/or Gottron's sign) is required if no [redacted] is available
   - OR
   - B. Total aggregated score ≥ 6.7 with [redacted]

     Note: The local [redacted] report will be used in the ACR/EULAR 2017 criteria to determine participant eligibility. Submission of the historical [redacted] or documentation of attempts to obtain results of historical [redacted] is required for randomized participants.
   - **AND (a or b)**

   a. Population 1: DM
   - Diagnosis of DM with DM rash current or historical
   - **OR**

   b. Population 2: ASIM
   - Anti-Jo-1 antibodies must be positive during Screening by central laboratory testing, **or**
   - One of following antibodies must be positive by historical testing: anti-PL-12, anti-PL-7, anti-KS, anti-EJ, anti-OJ, anti-ZO, anti-YRS(HA).

     Note: participants with a DM rash and positive for anti-Jo-1 antibodies during Screening will be considered part of Population 2. Participants with historical anti-Jo-1 who are negative by central laboratory anti-Jo-1 testing during Screening will not be eligible.
5. Currently active myositis with all the following (a, b, and c) during Screening:
   a. MMT8 score < 142
   b. At least 2 other abnormal CSM from the following list:
      - PtGDA ≥ 2 cm in a 10 cm visual analog scale (VAS)
      - PhGDA ≥ 2 cm in a 10 cm VAS
      - Extramuscular activity ≥ 2 cm in a 10 cm VAS
      - At least one muscle enzyme 1.5 times upper limit of normal (ULN)
      - HAQ-DI ≥ 0.5

   c. Global muscle damage score ≤ 5 on a 10 cm VAS on the MDI.

6. Participants should be on stable standard of care therapy if tolerated (a); if they are not able to tolerate it or have failed standard of care, medications should have washed out (b):
   a. Participants on corticosteroid treatment (up to 20 mg prednisone or equivalent per day) and/or up to 2, non-excluded, immunosuppressants on stable therapy for at least 4 weeks prior to Randomization **or**
   b. Participants with previous failure of response or previous intolerance to corticosteroid and at least 1 additional immunosuppressant drug, and with steroid/immunosuppressants washed out.
7. Participants should be willing to taper corticosteroid dose per protocol when stable or improving.

Sex and Contraceptive/Barrier Requirements

8. A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

   a. Is a woman of nonchildbearing potential (as defined in Appendix 3: Contraceptive and Barrier Guidance) **or**
   b. Is a woman of childbearing potential (as defined in Appendix 3: Contraceptive and Barrier Guidance), and:
      i. Has a negative serum pregnancy test at Screening and a negative urine pregnancy test at Day 1. Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5.

      ii. Agrees to use contraceptive methods that are highly effective (ie, has a failure rate of < 1%, as described in Appendix 3: Contraceptive and Barrier Guidance) from at least 4 weeks prior to Day 1 during the study intervention period and until at least 6 months after the last administration of IP or the end of the study, whichever is longer.

      iii. Agrees not to donate and/or retrieve eggs (ova, oocytes) for the purpose of reproduction during the study and 6 months after the last dose of IP.
      The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
9. Male participants are eligible to participate if they agree to the following during the study intervention period and for at least 3 months after the last dose of IP:

   – Refrain from donating fresh unwashed semen.

   Plus, either:

   – Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
   – OR

– Agree to use a male condom and should be advised of the benefit for a female partner to use a highly effective method of contraception. Effective methods of contraception are listed in Appendix 3: Contraceptive and Barrier Guidance.

Exclusion Criteria:

General Exclusion Criteria

1. Individuals involved in the conduct of the study, their employees, or immediate family members of such individuals.
2. Participation in another clinical study with an investigational drug within 4 weeks prior to Randomization or within 5 half-lives, whichever is longer.

Medical Conditions

3. Any condition that, in the opinion of the investigator or sponsor, would interfere with the evaluation of IP or interpretation of participant safety or study results.
4. Weight > 160 kg (352 pounds) at Screening.
5. History of allergy, hypersensitivity reaction, or anaphylaxis to any component of the IP or to a previous monoclonal antibody or human immunoglobulin therapy.
6. Breastfeeding or pregnant women or women who intend to become pregnant anytime from signing the ICF through 6 months after receiving the last dose of IP.
7. History of drug or alcohol abuse that, in the opinion of the investigator, might affect participant safety or compliance with visits, or interfere with other study assessments.
8. Major surgery within 8 weeks prior to Screening or elective surgery planned from Screening through the end of the study.
9. Spontaneous or induced abortion, still or live birth, or pregnancy ≤ 4 weeks prior to Screening through Randomization.
10. History of clinically meaningful cardiac disease including unstable angina, myocardial infarction, congestive heart failure within 6 months prior to Randomization; arrhythmia requiring active therapy, except for clinically insignificant extra systoles, or minor conduction abnormalities; or presence of clinically meaningful abnormality on ECG if, in the opinion of the investigator, it would increase the risk of study participation.
11. History of cancer within the past 5 years, except cutaneous basal cell or squamous cell carcinoma treated with curative therapy.
12. Any underlying condition that in the opinion of the investigator significantly predisposes the participant to infection (eg, hepatitis C).
13. Participant who has given > 50 mL of blood or plasma within 30 days of Screening or > 499 mL of blood or plasma within 56 days of Screening (during a clinical study or at a blood bank donation) or plans to give blood or plasma during their participation in the study or up to 6 months after the last administration of IP, whichever is longer.
14. Transfusion with blood, packed red blood cells, platelets or treatment with plasmapheresis, or plasma exchange within 8 weeks prior to Randomization and for the total duration of the study participation.

Laboratory Criteria

15. Known history of a primary immunodeficiency or an underlying condition, such as known human immunodeficiency virus (HIV) infection, or a positive result for HIV infection per central laboratory.
16. At Screening, any of the following per central laboratory tests (may be repeated once within the same screening period to confirm results prior to Randomization):
    - Total bilirubin > 1.5 × ULN (unless due to Gilbert's syndrome)
    - Neutrophil count < 1500/μL (or < 1.5×10^9/L)
    - Platelet count < 135,000/μL (or < 135×10^9/L)
    - Hemoglobin < 10 g/dL (or < 100 g/L)
    - Total lymphocyte count < 800/μL (or < 0.8×10^9/L)

Infections Criteria

17. All participants will undergo testing for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) during Screening.
    - Participants who are HBsAg positive are not eligible for the study.
    - Participants who are HBsAg negative and HBcAb positive will be reflex tested both for hepatitis B surface antibody (HBsAb) and hepatitis B virus (HBV) DNA. If HBsAb is positive and HBV DNA is negative, may be enrolled in the study; if HBsAb is negative or HBV DNA is positive, the participant is not eligible for the study.
18. Active tuberculosis (TB), or a positive IFNγ release assay (IGRA) test at Screening, unless documented history of appropriate treatment for active or latent TB according to local guidelines. Participants with an indeterminate IGRA test result can repeat the test, but if the repeat test is also indeterminate, they will be excluded.
19. Any severe herpes virus family infection (including Epstein-Barr virus, cytomegalovirus [CMV]) at any time prior to Randomization, including, but not limited to, disseminated herpes, herpes encephalitis, recent recurrent herpes zoster (defined as 2 episodes within the last 2 years), or ophthalmic herpes.
20. Any herpes zoster, CMV, or Epstein-Barr virus infection that was not completely resolved 12 weeks prior to Randomization.
21. Any of the following within 30 days prior to signing the ICF and through Randomization:
    - Clinically meaningful active infection in the opinion of the investigator (eg, hepatitis C), including ongoing, and chronic infection requiring antibiotics or antiviral medication (chronic nail infections are allowed).

      i. All participants will undergo testing for hepatitis C virus antibody (HCVAb) during Screening. Participants who are HCVAb positive will be reflex tested for hepatitis C virus (HCV) RNA. If HCV RNA is positive, the participant is not eligible for the study.

- Any infection requiring hospitalization or treatment with intravenous anti-infectives.
- A participant with a documented positive severe acute respiratory syndrome-coronavirus-2 test may be rescreened at least 2 weeks after a positive test if the participant is asymptomatic and at least 3 weeks after symptomatic coronavirus disease 2019 (COVID-19) illness.

22. Opportunistic infection requiring hospitalization or parenteral antimicrobial treatment within 2 years prior to Randomization.
23. Any acute illness or evidence of clinically meaningful active infection on Day 1.
24. Participants who have COVID-19 or other significant infection, or in the judgment of the investigator, may be at a high risk of COVID-19 or its complications should not be randomized.

Disease-Related Criteria

25. Significant organ system involvement or myositis damage (global muscle damage score > 5 on a 10 cm VAS scale on the MDI) that poses risks in the study or impedes assessments.
26. Diagnosis of immune-mediated necrotizing myopathy (IMNM) (positive anti-HMGR, anti-SRP, or antibody negative), inclusion body myositis (IBM) (including positive anti-cN1A), or drug-induced myositis.
27. Current musculoskeletal, joint, or inflammatory disease, including significant joint contractures or calcinosis that in the opinion of the investigator, could interfere with the muscle strength assessments and confound the disease activity assessments.
28. Wheelchair bound participants
29. Current inflammatory skin disease other than DM or ASIM that, in the opinion of the investigator, could interfere with the inflammatory skin assessments or confound the disease activity assessments.
30. Severe interstitial lung disease where respiratory symptoms limit participant function, or progressive pulmonary fibrosis.
31. Myositis in overlap with another connective tissue disease that precludes the accurate assessment of a treatment response (for example, difficulty in assessing muscle strength in a scleroderma patient with associated myositis).

Prior/Concomitant Therapy

32. Use of Janus kinase inhibitors within 4 weeks prior to Randomization.
33. Use of cyclophosphamide within 3 months prior to Randomization.
34. Use of IVIG within 4 weeks prior to Randomization.
35. Previous treatment with any biologic B-cell-depleting therapy (eg, rituximab, ocrelizumab, or ofatumumab) or other B-cell targeting therapy (eg, belimumab) within 3 months prior Randomization. B-cells should be detectable at lower limit of normal or greater per local laboratory after therapy with these treatments prior to Randomization.
36. Previous treatment with anti-BDCA2 [BIIB059] within 6 months prior to Randomization.

37. Participants who have received previous treatment with daxdilimab
38. Any biologic or antiproliferative agents if last dose was taken:
    - Within 4 weeks prior to Randomization, **or**
    - Within drug-specific 5 half-lives elimination period (if longer than 4 weeks) prior to Randomization.
39. Exposure to an experimental drug either 30 days, 5 half-lives of the agent, or twice the duration of the biological effect of the agent, whichever is longer, prior to Randomization and through the final study visit.
40. Receipt of a live-attenuated vaccine within 4 weeks prior to Randomization and through the final study visit.

Statistical Analyses:

[redacted]

Analysis Sets:

- Full Analysis Set: The Full Analysis Set will include all randomized participants and who receive any dose of IP in the study. Participants will be analyzed according to the treatment randomized. The efficacy analysis will be based on the Full Analysis Set.
- Safety Analysis Set: The Safety Analysis Set will include all participants who received any dose of IP in the study. Participants will be analyzed according to the treatment that they actually received. Safety, antidrug antibodies (ADA), and [redacted] analyses will be based on Safety Analysis Set.
- PK Analysis Set: The PK Analysis Set will include all participants who receive any dose of daxdilimab in the study and have at least one quantifiable serum PK observation post first dose. Participants will be analyzed according to the treatment that they actually received. The PK analysis will be based on the PK Analysis Set.

[redacted]



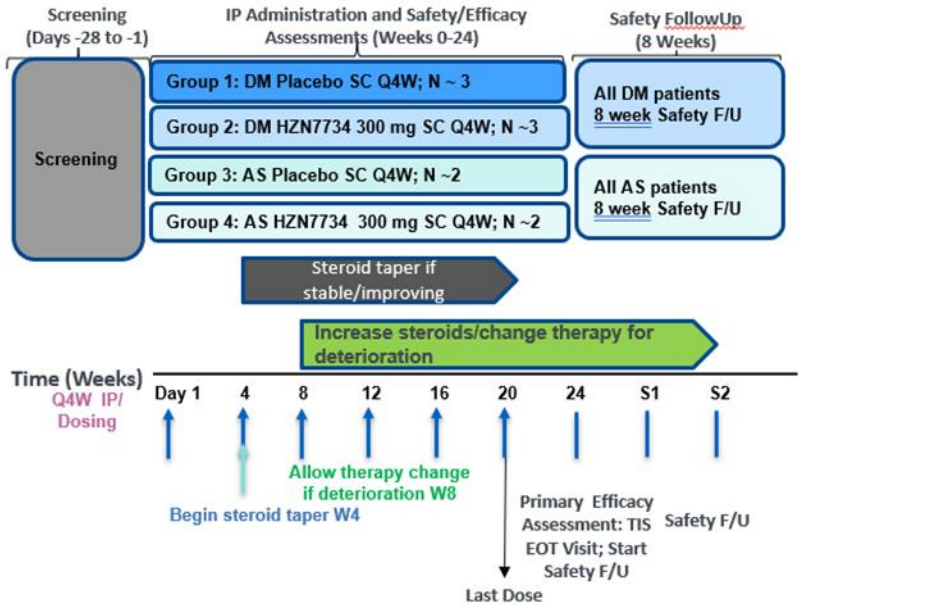
Data Monitoring/Other Committee: Yes

Participant safety will be continuously monitored by the external, independent Safety Data Monitoring Committee (SDMC), which includes safety signal detection at any time during the study. The SDMC is also responsible for supporting study integrity and interpretability based on their review of ongoing study conduct.

All safety data collected will be summarized and reviewed by the SDMC for agreement of next steps.

1.2 Schema

Figure 1 Study Diagram



Note: Participants who have received dosing beyond Week 20 will discontinue treatment and complete the procedures required at the EOT visit 4 weeks after the last dose and then complete the SFU (S1 and S2) visits

ASIM = anti-synthetase inflammatory myositis; DM = dermatomyositis; G = group; IP = investigational product; N = number of participants; Q4W = once every 4 weeks; SC = subcutaneously; SFU = safety follow-up; TIS = total improvement score.

1.3 Schedule of Activities

Table 1 provides the schedule of activities (SoA) to be performed at Screening, Treatment, and Safety Follow-Up (SFU).

Screening Evaluation

- The screening evaluation will only be performed after the participant has agreed to participate and has signed and dated the Informed Consent Form (ICF). No treatment or study-related procedures will be initiated before the ICF is signed.
- The screening evaluation will be performed according to the inclusion (Section 5.1) and exclusion (Section 5.2) criteria. If the participant fulfills all inclusion and no exclusion criteria, they may be enrolled in the study.

Treatment

Participants will be assigned to investigational product (IP) (ie, daxdilimab or placebo) by randomization at Day 1 visit, which will take place, at the latest, 28 days after successful Screening.

Unless otherwise specified, the study assessments scheduled on Day 1 must be performed before the administration of IP. The recommended order for performing the study assessments during the treatment period is as follows (applicable to all visits):

1. Collection of patient-reported outcomes
2. Physician assessments
3. Vital signs
4. 12-lead electrocardiograms (ECGs)
5. Blood draw

Patient-reported outcomes should be completed in the following order:



Table 1 Schedule of Activities

Period	**Screening[a]**	**Randomized Control Period**								**SFU**	
Week	**D -28 to -1**	[redacted]								**S1[c]**	**S2[d]**
Visit Window (Days)	**-**									**± 7**	**± 7**
Visit Number	**1**										
General Procedures											
Informed consent	X										
Medical history – include Raynaud's arthritis	X										
Inclusion/exclusion criteria review	X										
Demographic data	X										
Height	X										
Eligibility review[e]		X									
Randomization		X									
Patient-Reported Outcomes[f]											
[redacted]											
Physician Assessments											

PhGDA	X	X	X	X	X	X	X	X	X		X
MMT8 bilateral	X	X	X	X	X	X	X	X	X		X
[redacted]											
CDASI		X	X	X	X			X	X		
Steroid taper if stable or improving			X	X	X	X	X				
[redacted]											
Physical examination[i]	X							X	X		
Weight	X	X						X	X		
Vital signs[j]	X	X	X	X	X	X	X	X	X		X
12-lead ECG[k]	X							X	X		
[redacted]											
Laboratory Assessments											
TB assessment[n]	X										
Anti Jo-1 antibody	X										
Serum virology[o]	X										
Estradiol and FSH[p]	X										
Pregnancy (serum βhCG) test[q]	X										
Pregnancy (urine) test[q]		X	X	X	X	X	X	X	X		X
Routine chemistry[r]	X	X	X	X	X			X	X		X

Hematology (CBC with differential)	X	X	X	X	X			X	X		X
Urinalysis[s]	X	X						X	X		
Enzymes: aldolase, CK, ALT, AST, LDH	X	X	X	X	X	X	X	X	X		X
[redacted]											
MSA		X						X	X		
[redacted]											
Daxdilimab PK (serum)[t]		X	X	X	X	X		X	X		X
[redacted]											
Administration of IP											
Administration of IP[w]		X	X	X	X	X	X				
Local injection tolerability[x]		X	X	X	X	X	X	X	X		
Concomitant medications	Continuous										
AEs, SAEs, and/or AESIs	Continuous										

Note: The Schedule of Activities for the prior Protocol, Version 1.1 Amendment 1 can be referenced in Section 10.7.

AE = adverse event; ADA = antidrug antibody; AESI = AE of special interest; ALT = alanine transaminase; AST = aspartate transaminase; βhCG = βhuman chorionic gonadotropin; CBC = complete blood count; CDASI = cutaneous dermatomyositis disease area and severity index; CK = creatine kinase; DC = dendritic cells; ECG = electrocardiogram; [redacted]; FSH = follicle stimulating hormone; [redacted] IFN = interferon; IP = investigational product; LDH = lactate dehydrogenase; [redacted] MMT = manual muscle testing; [redacted]; MSA = myositis-specific antibodies; [redacted] PhGDA = physician global disease activity; PK = pharmacokinetics; [redacted] S1=Safety Visit 1; S2=Safety Visit 2:SAE = serious AE; [redacted]; SFU = safety follow-up; [redacted]; TB = tuberculosis; Wk = week; X = to be performed.

a With approval of the medical monitor, Screening could be extended for 2 weeks in the event of delayed laboratory results.
b EOT/ET visit will only occur for participants who have received dosing beyond Week 20 or who have prematurely discontinued IP administration.
c Safety Visit 1 (S1) visit may be performed as a phone call to the participant.
d Additional safety follow-up assessments beyond S2 may be discussed with Medical Monitor as needed.
e Participant eligibility (based on Screening assessments, including nonlaboratory-based assessments at Baseline [Day 1] as per the inclusion and exclusion criteria) must be checked on Day 1 prior to Randomization.
f Questionnaires should be completed before any other procedures are performed.
[redacted]
i A complete physical examination at Screening and at Weeks 24 and EOT/ET including assessment of head, ears, eyes, nose, throat, lungs, heart, abdomen, skin, and extremities.
j Vital signs include systolic and diastolic blood pressure obtained after at least 5 minutes at rest in a seated position, heart rate, respiratory rate (breaths/min), and body temperature.
k Should be performed after 10 minutes rest in supine position and after vital signs are collected.
[redacted]
n The results of an IFNγ release assay (ie, QuantiFERON-TB Gold Plus or T-SPOT) performed within 12 weeks of the Screening visit (if available) are acceptable, provided there is no reason to suspect any re-exposure.
o Serum virology does not have to be repeated if performed within 12 weeks prior to Screening (eg, Rescreening). Table 8 shows a complete list of serology assessments.
p To confirm postmenopausal status, as appropriate. Estradiol and FSH tests do not have to be repeated if performed within 12 weeks prior to Screening (eg, Rescreening).
q In women of childbearing potential or women who are postmenopausal for less than 2 years prior to Screening, have nontherapy-induced amenorrhea for less than 12 months prior to Screening, or are not surgically sterile (absence of fallopian tubes, ovaries and/or uterus).
r Go to Table 8 for a complete list of routine laboratory assessments.
s Urine collection can be postponed for up to 14 days in women with menstrual bleeding or a urinary tract infection at the scheduled visit. Go to Table 8 for a complete list of routine urinalysis assessments.
t Serum daxdilimab PK will be obtained at Day 1 at approximately 2 hours or longer postdose, predose on Day 1 and Weeks 4, 8, 12, 16, and any time on Weeks 24 and/or EOT/ET visit.
[redacted]
v Collection at Day 1 (required) and at-home collection (fingerstick) at 1 week (optional).
w The visit window for the IP administration is ± 3 days. If a visit and dosing is outside the visit window, a protocol deviation will be noted, and IP may be administered within the -13 days +14 days as a remedial dosing window. Except for local injection tolerability (footnote x) on days of administration of IP, all procedures and blood sampling must be collected before the administration.
x To be performed 30 minutes postdose (can be performed any time at Week 24 and/or EOT/ET visit as no IP is administered).

2 INTRODUCTION

2.1 Study Rationale

Idiopathic inflammatory myopathies, including dermatomyositis (DM) and anti-synthetase inflammatory myositis (ASIM), can result in permanent muscle damage with weakness if not controlled promptly. Currently, corticosteroids, intravenous immunoglobulin (IVIG), and other immune modulators are used for treatment, but these medications are also associated with noticeable side effects. In addition, some patients do not achieve timely control of their disease with these therapies. This, together with the burden of their side effects, yields the clinical need for a therapy to treat these patients.

Daxdilimab is being developed for the treatment of multiple autoimmune disorders in which plasmacytoid dendritic cells (pDCs) are believed to contribute to the pathogenesis, including DM and ASIM. The inflammatory response in these disorders is characterized by the production of large amounts of type I interferons (IFNs) by pDCs (Chakka et al, 2021; Crow et al, 2019). Daxdilimab has the capacity to specifically bind to the surface of pDCs, induce apoptosis, and deplete pDCs in vivo. It is hypothesized that the depletion of pDCs induced by daxdilimab will reduce disease activity in patients with DM or ASIM.

Phase 1 clinical studies have tested the safety, tolerability, pharmacokinetics (PK), [redacted] and immunogenicity of different doses of daxdilimab in participants with autoimmune disorders, such as DM, polymyositis (PM), Sjogren's syndrome, systemic lupus erythematosus (SLE), cutaneous lupus erythematosus (CLE) or systemic sclerosis. Additionally, Phase 2 studies are being performed or planned to test the safety and efficacy of daxdilimab in treating moderate to severely active SLE, alopecia areata, and discoid lupus erythematosus, which yields the need for a similar study in participants with DM or ASIM.

2.2 Background

The inflammatory response in autoimmune disorders in which pDCs are implicated, such as in DM and ASIM, is characterized by the production of large amounts of type I IFNs by pDCs (Chakka et al, 2021; Crow et al, 2019). In DM, pDCs constitute up to 50% of CD4+ cell infiltrate in inflamed muscle (Greenberg et al, 2005). A recent study examining the gene signatures in inflamed muscles reported differential expression of IFN genes in different types of myositis, being high for type I IFN in DM and moderate in ASIM (Pinal-Fernandez et al, 2019). Furthermore, skin lesions from DM and ASIM patients showed type I IFN regulation and strong pDC infiltration (Patel et al, 2021).

Daxdilimab (previously known as MEDI7734, VIB7734, and HZN-7734) is an immunoglobulin (Ig) G1 lambda afucosylated monoclonal antibody (mAb) with the capacity to specifically bind to immunoglobulin-like transcript 7 (ILT7), a cell-surface protein unique to pDCs in human and nonhuman primates. Binding to ILT7 on the surface of pDCs leads to the recruitment of macrophages and natural killer cells, thus inducing apoptosis and depletion of pDCs in vivo. The afucosylation of daxdilimab is designed to enhance its potency for antibody—dependent cellular cytotoxicity against pDCs. Since pDCs are the major cell type that secretes type I IFNs in response to nucleic acid-containing immune complexes, it is hypothesized that, by depleting pDCs, daxdilimab has the potential to reduce disease activity in patients with DM or ASIM. Data

from Phase 1 (Furie et al, 2019a), Phase 2 (Merrill et al, 2018), and Phase 3 (Furie et al, 2019b; Morand et al, 2019) studies with other type-I-IFN-blocking agents and pDCs antagonists have demonstrated improvement in SLE disease activity, supporting the rationale for blocking the IFN pathways and pDCs in patients with primary DM or ASIM.

Phase 1 clinical studies (D6080C00001 and VIB7734.P1b.S1) to evaluate the safety, tolerability, PK, PD, and immunogenicity of daxdilimab in participants with DM, PM, Sjogren's syndrome, SLE, CLE, or systemic sclerosis have been completed. Additionally, Phase 2 studies to test the safety and efficacy of daxdilimab in treating moderate to severely active SLE (VIB7734.P2.S1), alopecia areata (HZNP-DAX-201), and discoid lupus erythematosus (HZNP-DAX-202) are being performed or planned.

Although corticosteroids, IVIG, and other immune modulators are used for treatment of DM and ASIM, these medications are also associated with noticeable side effects including risk for diabetes, osteoporosis, cataracts, opportunistic infections, and thrombosis. In addition, some patients do not achieve timely control of their disease with these therapies. This, together with the burden of their side effects, yields the clinical need for new therapies to treat these patients.

The need for new therapies and for a dedicated study to ascertain the benefit-risk of daxdilimab justifies running a study that will evaluate the efficacy and safety of daxdilimab in participants with inadequately controlled DM or ASIM.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of daxdilimab may be found in the Investigator's Brochure (IB).

2.3.1 Risk Assessment

Two Phase 1 clinical studies (D6080C00001 and VIB7734.P1b.S1) to evaluate the safety, tolerability, PK, PD, and immunogenicity of daxdilimab in participants with a range of autoimmune disorders have been completed. An additional Phase 1 study (VIB7734.P1.S2) to assess the ability of daxdilimab to prevent immune-mediated acute lung injury related to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection has been terminated. Finally, one Phase 2 study to test the safety and efficacy of daxdilimab in treating moderate to severely active SLE (VIB7734.P2.S1) is ongoing.

In Study D6080C00001, a Phase 1, first-in-human, single-ascending dose study, single subcutaneous (SC) doses of daxdilimab (1, 5, 15, 50, or 150 mg) or placebo were administered to 36 adult participants with DM, PM, Sjogren's syndrome, SLE, or systemic sclerosis. No serious adverse events (SAEs) occurred that were considered related to daxdilimab. Two participants had treatment-emergent adverse events (TEAEs) considered related to daxdilimab by the investigator: one participant in the placebo group had nausea (Grade 1) and one participant in the daxdilimab 50 mg group had tongue discoloration (Grade 1). The most common AEs reported in the daxdilimab-treated participants were diarrhea (11.5%) and upper respiratory tract infection (11.5%). There was no imbalance of AEs between the daxdilimab and placebo groups. No injection site reactions or hypersensitivity reactions were reported. No antidrug antibodies (ADAs) occurred.

In Study VIB7734.P1b.S1, a Phase 1b, multiple-ascending dose study, 3 monthly SC doses of daxdilimab (5, 50, or 150 mg) or placebo were administered to 31 adult participants with DM, PM, Sjogren's syndrome, SLE, systemic sclerosis or CLE. Sixteen of 22 (72.7%) participants treated with daxdilimab and 6 of 9 (66.7%) participants treated with placebo experienced at least one TEAE. There were no deaths in the study. One placebo-treated participant and no daxdilimab-treated participants experienced treatment-emergent SAEs (TESAEs). No participant experienced an AE leading to treatment discontinuation. No treatment-emergent ADA observed in participants treated with daxdilimab.

In Study VIB7734.P1.S2, a Phase 1, double-blind, placebo-controlled proof of concept study, a single 150 mg SC dose of daxdilimab or placebo was administered to 10 adult participants with SARS-CoV-2 infection with lower respiratory tract involvement and signs of a hyperinflammatory reaction. The most common TEAEs among the 5 participants treated with daxdilimab were infections and infestations, gastrointestinal disorders, respiratory, thoracic, and mediastinal disorders, and skin and subcutaneous tissue disorders. Most of these TEAEs were mild and only 2 participants taking daxdilimab had a severe TEAEs.

Study VIB7734.P2.S1 was a randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the safety and efficacy of daxdilimab in adults with moderate to severely active SLE. The study enrolled 214 participants into 3 groups. Participants received placebo, daxdilimab 200 mg Q4W, or daxdilimab 200 mg every 12 weeks (Q12W) by SC injection. During the study, 107 of 143 (74.8%) daxdilimab-treated participants and 49 of 71 (69.0%) placebo-treated participants experienced at least one TEAE. There was one death in the study, which was not considered to be related to the IP by the Investigator. One SAE (Grade 2 pneumonia), reported in a participant in the daxdilimab 200 mg Q4W group, was considered to be related to IP by the Investigator. One additional SAE (Grade 3 herpes zoster), reported in a participant in the daxdilimab 200 mg Q4W group, was considered related to IP by the Sponsor. Eight daxdilimab-treated participants and one placebo-treated participant experienced events leading to treatment discontinuation. Across all treatment groups, TEAEs were most frequently reported in the system organ class of Infections and infestations (52.4% of daxdilimab-treated participants and 46.5% of placebo-treated participants). For the daxdilimab-treated participants, the most frequently reported TEAEs by preferred term were COVID-19 (13.3%) and urinary tract infection (10.5%); the majority of the TEAEs by preferred term were only reported in 1 (0.7%) or 2 (1.4%) participants. No relationship was observed in the frequency of TEAEs for the 2 dose frequencies studied.

Study HZNP-DAX-201 is an open-label, proof-of-concept trial to assess the preliminary efficacy, safety, tolerability, PK, and PD of daxdilimab in participants with moderate to severe alopecia areata. The study enrolled 30 participants who received daxdilimab 300 mg Q4W by SC injection for 32 weeks (9 doses). As of the Week 24 primary analysis (data cut-off date 08 Sep 2023), 14 participants had completed the treatment period and 9 participants had completed the trial. As of 08 Sep 2023, 21 of the 30 (70.0%) daxdilimab-treated participants experienced at least one TEAE. There were no deaths, no TESAEs, and no AEs leading to treatment discontinuation. Treatment-emergent AEs were most frequently reported in the system organ class of Infections and infestations (46.7%) and General disorders and administration site conditions (30.0%). The most frequently reported TEAEs by preferred term were injection site

reaction (20.0%) and nasopharyngitis (16.7%); all other TEAEs by preferred term were reported in 1 (3.3%) or 2 (6.7%) participants.

To date, injection site reactions have been determined to be a non-important identified risk for daxdilimab.

Important potential risks for daxdilimab include viral infection and viral reactivation, opportunistic infection, malignancy (other than non-melanoma skin cancer), and hypersensitivity reactions including anaphylaxis. Other potential risks include vaccine interaction, drug-drug interactions, and reproductive toxicity.

A detailed description of the chemistry, pharmacology, efficacy, and safety of daxdilimab is provided in the current version of the IB.

2.3.1.1 COVID-19 Risk Assessment

An additional risk of study participation includes potential exposure of the participant to SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19), by visiting the study site. Sites must have a plan in place to minimize this risk. Although testing for COVID-19 prior to the first administration of IP is not required, the investigator may choose to have this test performed locally in accordance with his/her judgment based on participant risk. This test is not provided through the study's central laboratory because the result of a test at Screening would not be appropriately timed to be relevant to the first administration of IP.

To minimize risk to participants, study sites will be activated to initiate participant enrollment only after review of local COVID-19 disease incidence, prevalence, containment measures, availability of healthcare resources, ability to monitor site activities, and the presence of a site plan to minimize participant exposure to SARS-CoV-2 during site visits have been confirmed.

Data from Study VIB7734.P1.S2 showed there were no differences between daxdilimab and placebo on preventing an immune-mediated acute lung injury related to SARS-CoV-2 infection.

The current available evidence does not suggest a difference in COVID-19 infection risk in persons with DM or ASIM compared to the general population except for what is known about the increased risk that may be associated with comorbid disease and use of immunosuppressive treatment.

The investigator will assess the benefit-risk for each individual participant for determination of suitability for enrollment based on known risk factors for COVID-19 severity and possible or known exposure to SARS-CoV-2.

Because of the evolving spread and containment measures of COVID-19, ongoing risk assessment will be required of participating study sites and investigators.

In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

2.3.2 Benefit Assessment

In this Phase 2 study, it is hypothesized that participants with inadequately controlled DM or ASIM may see an improvement in their condition and their quality of life as a result of participating in the study.

Participation in this study may help generate future benefit for larger groups of patients with DM/ASIM if daxdilimab is proven to be successful in treating this disease.

2.3.3 Overall Benefit-Risk Conclusion

All quality, pharmacology, and toxicology data, and safety and tolerability data demonstrated in nonclinical studies are considered sufficient to expect a positive benefit/risk ratio for the treatment of participants with inadequately controlled DM or ASIM with daxdilimab, and therefore to initiate this study.

The risk to participants in this study will be minimized by compliance with the eligibility criteria, proper study design, and close monitoring.

Accounting for the measures taken to minimize risk to participate in this study, the potential risks identified in association with daxdilimab are justified by the anticipated benefits that may be afforded to participants with inadequately controlled DM or ASIM.

3 OBJECTIVES AND ENDPOINTS

Study objectives and endpoints are presented in Table 2 and are the same for DM and ASIM, with an independent analysis of the 2 populations.

Table 2 Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
• To evaluate the effect of daxdilimab compared with placebo in reducing disease activity at Week 24.	• TIS at Week 24.
Secondary Efficacy	
• To evaluate the effect of daxdilimab compared with placebo in reducing disease activity at Week 24.	• Proportion of participants with improvement of TIS ≥ 40 and without deterioration at 2 consecutive visits at 24 weeks. • Proportion of participants with improvement of TIS ≥ 20 and without deterioration at 2 consecutive visits at 24 weeks.
• To evaluate the effect of daxdilimab compared with placebo on skin symptoms at Week 24.	• Change in the CDASI activity score from Baseline (Day 1) to Week 24.
• To evaluate the effect of daxdilimab on decreasing the use of corticosteroid at Week 24.	• Proportion of participants on an OCS dose ≥ 10 mg of prednisone or equivalent at Baseline who achieve a clinically meaningful reduction in the OCS dose: either a 25% decrease or an OCS dose of 7.5 mg/day of prednisone or equivalent at Week 24.
Pharmacokinetics and Immunogenicity	
• To characterize the PK and immunogenicity of daxdilimab in participants.	• Serum concentration of daxdilimab over time. • Prevalence at Baseline and incidence and titer of ADA directed against daxdilimab over time.
Safety	
• To evaluate the safety and tolerability of daxdilimab in participants.	• Incidence of TEAEs • Incidence of TESAEs • Incidence of TEAESIs: hypersensitivity reaction, including anaphylaxis, herpes zoster infection, severe (CTCAE Grade 3 or higher) viral infection/reactivation, opportunistic infection, and malignancy (except non-melanoma skin cancer).

Table 2 Objectives and Endpoints

Objectives	Endpoints
Exploratory	
[redacted]	

Table 2 Objectives and Endpoints

Objectives	Endpoints
[redacted]	

ADA = antidrug antibodies; CDASI = cutaneous dermatomyositis disease area and severity index; CSM = core set measures; CTCAE = common terminology for adverse events; [redacted]; IFN = interferon [redacted] pDCs = plasmacytoid dendritic cells; [redacted] PK = pharmacokinetics; [redacted] TEAEs = treatment-emergent adverse events; TESAEs = treatment-emergent serious adverse events; TEAESIs = treatment-emergent adverse events of special interest; TIS = total improvement score

4 STUDY DESIGN

4.1 Overall Design

This study is a Phase 2, randomized, double-blind, placebo-controlled, proof of concept study to assess the efficacy and safety of daxdilimab in participants aged ≥ 18 to ≤ 75 years with DM or ASIM.

The study will enroll 2 idiopathic inflammatory myositis participant populations (Figure 1):

- Population 1 or DM: participants with DM with definite or probable myositis according to the American College of Rheumatology/European League Against Rheumatism 2017 (ACR/EULAR 2017) (Lundberg et al, 2019) criteria and a DM rash.
- Population 2 or ASIM: participants with ASIM with definite or probable myositis according to ACR/EULAR 2017 criteria and a positive ASIM associated antibody.

Approximately 10 participants will be randomized by population in a 1:1 ratio (2-3 participants per group) to receive IP (daxdilimab 300 mg or placebo) by SC injection Q4W:

- Group 1: DM placebo
- Group 2: DM daxdilimab 300 mg
- Group 3: ASIM placebo
- Group 4: ASIM daxdilimab 300 mg

Randomization will take place, at the latest, 28 days after successful screening, and it will be stratified by Manual Muscle Testing 8 (MMT8) score (≤ 120 vs > 120) at Baseline (Day 1).

The estimated total study duration, from Screening to the end of the SFU period, will be up to approximately 36 weeks for participants in the randomized (first 24 weeks) portion of the study at amendment approval, and up to 60 weeks for participants in the Open-label extension (Table 1):

1. Screening period of approximately 4 weeks (Days -28 to -1)
2. Treatment period from Day 1 through Week 24
   - Randomization (double-blinded) on Day 1
   - Administration of IP from Day 1 through Week 20
   - Efficacy and safety assessments Q4W through Week 24
   - Consisting of a randomized control period (RCP) (double-blinded) from Day 1 through Week 24:
     a. Randomized control period (double-blinded) from Day 1 through Week 24

        Primary assessment of the efficacy endpoints will be done at Week 24.

     b. Open-Label extension from Week 24 through Week 48

        No additional participants will enter the Open-label extension. Participants currently in the Open-label extension will stop dosing and perform the EOT/ET visit and safety follow-up visits. The schedule of activities for these visits are listed under the EOT/ET visit and Safety 1 and Safety 2 visits.

Participants who have not yet entered the open-label extension will complete the Week 24 visit followed by safety follow up visits.

Participants who have received dosing beyond Week 20 will discontinue treatment and complete the procedures required at the EOT visit 4 weeks after the last dose and then complete the SFU visits.

3. Safety Follow-Up period of 8 weeks

All administrations of IP will be administered by an unblinded pharmacist or nurse at the clinic and the participant will be observed for at least 60 minutes after the first and second doses and for 20 minutes for all subsequent doses.

Efficacy assessments will include a series of scores, scales, and other measurements to assess disease activity, damage, and improvement (Section 8.2).

Safety assessments will include measurement of physical examinations, vital signs, ECGs, pregnancy testing, local injection tolerability, monitoring of hematology, blood chemistry, and urinalysis (Section 8.3), and monitoring and recording of all AEs (Section 8.4).

Patient-reported outcomes will be used to record the wellbeing and quality of life of the participants during the study.

To characterize the PK, PD, and immunogenicity of daxdilimab, blood samples from all participants, and optional muscle and/or skin biopsies from those who agree, will be collected.

Unless otherwise specified, the study assessments scheduled on Day 1 must be performed before the administration of IP; patient-reported outcomes will be performed first, followed by the physician assessments, measurement of vital signs, and laboratory assessments. The SoA and the order in which they should be performed are in Section 1.3.

In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

The study will be conducted on an outpatient basis globally.

4.2 Scientific Rationale for Study Design

The proposed Phase 2 study design is considered appropriate for assessing the safety and efficacy of daxdilimab in participants with DM or ASIM.

4.3 Justification for Dose

[redacted]



4.4 End-of-Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the study globally.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA.

Internal Use Only General and Administrative

5 STUDY POPULATION

Participants eligible for this study will have DM or ASIM.

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

5.1 Inclusion Criteria

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

Informed Consent

1. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the United States) obtained from the participant/legal representative prior to performing any protocol-related procedures, including screening evaluations.
2. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the study.

Age and Sex

3. Adult men or women ≥ 18 and ≤ 75 years of age at the time of signing the ICF.

Type of Participant and Disease Characteristics

4. A diagnosis of definite or probable myositis according to ACR/EULAR 2017 criteria (A OR B):
   - A. Total aggregated score ≥ 5.5 without a [redacted]

     Note: Pathognomonic skin rash (such as mechanic's hands, heliotrope rash, Gottron's papules and/or Gottron's sign) is required if no [redacted] is available.
   - OR
   - B. Total aggregated score ≥ 6.7 with [redacted]

     Note: The local [redacted] report will be used in the ACR/EULAR 2017 criteria to determine participant eligibility. Submission of the historical [redacted] or documentation of attempts to obtain results of historical [redacted] is required for randomized participants.
   - **AND (a or b)**

   a. Population 1: DM

   - Diagnosis of DM with DM rash current or historical
   - **OR**

b. Population 2: ASIM

– Anti-Jo-1 antibodies must be positive during Screening by central laboratory testing, **or**
– One of following antibodies must be positive by historical testing: anti-PL-12, anti-PL-7, anti-KS, anti-EJ, anti-OJ, anti-ZO, anti-YRS(HA).

Note: participants with a DM rash and positive for anti-Jo-1 antibodies during Screening will be considered part of Population 2. Participants with historical anti-Jo-1 who are negative by central laboratory anti-Jo-1 testing during Screening will not be eligible.

5. Currently active myositis with all the following (a, b, and c) during Screening:
   a. MMT8 score < 142
   b. At least 2 other abnormal core set measures (CSM) from the following list:
      - PtGDA ≥ 2 cm in a 10 cm visual analog scale (VAS)
      - Physician's Global Disease Activity (PhGDA) ≥ 2 cm in a 10 cm VAS
      - Extramuscular activity ≥ 2 cm in a 10 cm VAS
      - At least one muscle enzyme 1.5 times upper limit of normal (ULN)
      - HAQ-DI ≥ 0.5
   c. Global muscle damage score ≤ 5 on a 10 cm VAS on the myositis damage index (MDI)
6. Participants should be on stable standard of care therapy if tolerated (a); if they are not able to tolerate it or have failed standard of care, medications should have washed out (b):
   a. Participants on corticosteroid treatment (up to 20 mg prednisone or equivalent per day) and/or up to 2, non-excluded, immunosuppressants on stable therapy (Table 5) for at least 4 weeks prior to Randomization **or**
   b. Participants with previous failure of response or previous intolerance to corticosteroid and at least 1 additional immunosuppressant drug, and with steroid/immunosuppressants washed out (Table 5).
7. Participants should be willing to taper corticosteroid dose per protocol when stable or improving.

Sex and Contraceptive/Barrier Requirements

8. A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

   a. Is a woman of nonchildbearing potential (WONCBP, as defined in Appendix 3: Contraceptive and Barrier Guidance) **or**
   b. Is a woman of childbearing potential (WOCBP, as defined in Appendix 3: Contraceptive and Barrier Guidance) and:

i. Has a negative serum pregnancy test at Screening and a negative urine pregnancy test at Day 1. Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5.

ii. Agrees to use contraceptive methods that are highly effective (ie, has a failure rate of < 1%, as described in Appendix 3: Contraceptive and Barrier Guidance) from at least 4 weeks prior to Day 1 during the study intervention period and until at least 6 months after the last administration of IP or the end of the study, whichever is longer.

iii. Agrees not to donate and/or retrieve eggs (ova, oocytes) for the purpose of reproduction during the study and 6 months after the last dose of IP.
The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

9. Male participants are eligible to participate if they agree to the following during the study intervention period and for at least 3 months after the last dose of IP:

   – Refrain from donating fresh unwashed semen.

   Plus, either:

   – Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
   – **OR**
   – Agree to use a male condom and should be advised of the benefit for a female partner to use a highly effective method of contraception. Effective methods of contraception are listed in Appendix 3: Contraceptive and Barrier Guidance.

5.2 Exclusion Criteria

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

General Exclusion Criteria

1. Individuals involved in the conduct of the study, their employees, or immediate family members of such individuals.
2. Participation in another clinical study with an investigational drug within 4 weeks prior to Randomization or within 5 published half-lives, whichever is longer.

Medical Conditions

3. Any condition that, in the opinion of the investigator or sponsor, would interfere with the evaluation of IP or interpretation of participant safety or study results.
4. Weight > 160 kg (352 pounds) at Screening.
5. History of allergy, hypersensitivity reaction, or anaphylaxis to any component of the IP or to a previous mAb or human Ig therapy.

6. Breastfeeding or pregnant women or women who intend to become pregnant anytime from signing the ICF through 6 months after receiving the last dose of IP.
7. History of drug or alcohol abuse that, in the opinion of the investigator, might affect participant safety or compliance with visits, or interfere with other study assessments.
8. Major surgery within 8 weeks prior to Screening or elective surgery planned from Screening through end of study.
9. Spontaneous or induced abortion, still or live birth, or pregnancy ≤ 4 weeks prior to Screening through Randomization.
10. History of clinically meaningful cardiac disease including unstable angina, myocardial infarction, congestive heart failure within 6 months prior to Randomization; arrhythmia requiring active therapy, except for clinically insignificant extra systoles, or minor conduction abnormalities; or presence of clinically meaningful abnormality on ECG if, in the opinion of the investigator, it would increase the risk of study participation.
11. History of cancer within the past 5 years except cutaneous basal cell or squamous cell carcinoma treated with curative therapy.
12. Any underlying condition that in the opinion of the investigator significantly predisposes the participant to infection (eg, hepatitis C).
13. Participant who has given > 50 mL of blood or plasma within 30 days of Screening or > 499 mL of blood or plasma within 56 days of Screening (during a clinical study or at a blood bank donation) or plans to give blood or plasma during their participation in the study or up to 6 months after the last administration of IP, whichever is longer.
14. Transfusion with blood, packed red blood cells, platelets or treatment with plasmapheresis, or plasma exchange within 8 weeks prior to Randomization and for the total duration of the study participation.

Laboratory Criteria

15. Known history of a primary immunodeficiency or an underlying condition, such as known human immunodeficiency virus (HIV) infection, or a positive result for HIV infection per central laboratory.
16. At Screening, any of the following per central laboratory tests (may be repeated once within the same screening period to confirm results prior to Randomization):
    - Total bilirubin > 1.5 × ULN (unless due to Gilbert's syndrome)
    - Neutrophil count < 1500/μL (or < 1.5×10^9/L)
    - Platelet count < 135,000/μL (or < 135×10^9/L)
    - Hemoglobin < 10 g/dL (or < 100 g/L)
    - Total lymphocyte count < 800/μL (or < 0.8×10^9/L)

Infections Criteria

17. All participants will undergo testing for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) during Screening.
    - Participants who are HBsAg positive are not eligible for the study.

- Participants who are HBsAg negative and HBcAb positive will be reflex tested both for hepatitis B surface antibody (HBsAb) and hepatitis B virus (HBV) DNA. If HBsAb is positive and HBV DNA is negative, may be enrolled in the study; if HBsAb is negative or HBV DNA is positive, the participant is not eligible for the study.

18. Active tuberculosis (TB), or a positive IFN-γ release assay (IGRA) test at Screening, unless documented history of appropriate treatment for active or latent TB according to local guidelines. Participants with an indeterminate IGRA test result can repeat the test, but if the repeat test is also indeterminate, they will be excluded.
19. Any severe herpes virus family infection (including Epstein-Barr virus, cytomegalovirus [CMV]) at any time prior to Randomization, including, but not limited to, disseminated herpes, herpes encephalitis, recent recurrent herpes zoster (defined as 2 episodes within the last 2 years), or ophthalmic herpes.
20. Any herpes zoster, CMV, or Epstein-Barr virus infection that was not completely resolved 12 weeks prior to Randomization.
21. Any of the following within 30 days prior to signing the ICF and through Randomization:

    - Clinically meaningful active infection in the opinion of the investigator (eg, hepatitis C), including ongoing, and chronic infection requiring antibiotics or antiviral medication (chronic nail infections are allowed).

      i. All participants will undergo testing for hepatitis C antibody (HCVAb) during Screening. Participants who are HCVAb positive will be reflex tested for hepatitis C virus (HCV) RNA. If HCV RNA is positive, the participant is not eligible for the study.

    - Any infection requiring hospitalization or treatment with intravenous anti-infectives.
    - A participant with a documented positive SARS-CoV-2 test may be rescreened at least 2 weeks after a positive test if the participant is asymptomatic and at least 3 weeks after symptomatic COVID-19 illness.

22. Opportunistic infection requiring hospitalization or parenteral antimicrobial treatment within 2 years prior to Randomization.
23. Any acute illness or evidence of clinically meaningful active infection on Day 1.
24. Participants who have COVID-19 or other significant infection, or in the judgment of the investigator, may be at a high risk of COVID-19 or its complications should not be randomized.

Disease-Related Criteria

25. Significant organ system involvement or myositis damage (global muscle damage score > 5 on a 10 cm VAS scale on the MDI) that poses risks in the study or impedes assessments.

26. Diagnosis of immune-mediated necrotizing myopathy (IMNM) (positive anti-HMGR, anti-SRP, or antibody negative), inclusion body myositis (IBM) (including positive anti-cN1A), or drug-induced myositis.
27. Current musculoskeletal, joint, or inflammatory disease, including significant joint contractures or calcinosis that in the opinion of the investigator, could interfere with the muscle strength assessments and confound the disease activity assessments.
28. Wheelchair bound participants
29. Current inflammatory skin disease other than DM or ASIM that, in the opinion of the investigator, could interfere with the inflammatory skin assessments or confound the disease activity assessments.
30. Severe interstitial lung disease where respiratory symptoms limit participant function or progressive pulmonary fibrosis per Raghu et al, 2022.
31. Myositis in overlap with another connective tissue disease that precludes the accurate assessment of a treatment response (for example, difficulty in assessing muscle strength in a scleroderma patient with associated myositis).

Prior/Concomitant Therapy

32. Use of Janus kinase inhibitors within 4 weeks prior to Randomization.
33. Use of cyclophosphamide within 3 months prior to Randomization.
34. Use of IVIG within 4 weeks prior to Randomization.
35. Previous treatment with any biologic B-cell-depleting therapy (eg, rituximab, ocrelizumab, or ofatumumab) or other B-cell targeting therapy (eg, belimumab) within 3 months prior Randomization. B-cells should be detectable at lower limit of normal or greater per local laboratory after therapy with these treatments prior to Randomization.
36. Previous treatment with anti-BDCA2 [BIIB059] within 6 months prior to Randomization.
37. Participants who have received previous treatment with daxdilimab
38. Any biologic or antiproliferative agents if last dose was taken:
    - Within 4 weeks prior to Randomization, **or**
    - Within drug-specific 5 half-lives elimination period (if longer than 4 weeks) prior to Randomization.
39. Exposure to an experimental drug either 30 days, 5 half-lives of the agent, or twice the duration of the biological effect of the agent, whichever is longer, prior to Randomization and through the final study visit.
40. Receipt of a live-attenuated vaccine within 4 weeks prior to Randomization and through the final study visit.

5.3 Lifestyle Considerations

In this study, there will be no food, caffeine, alcohol, and tobacco restrictions. Participants will only be asked to abstain from strenuous exercise for 24 to 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during study visits (eg, watching television, reading).

5.4 Screen Failures

A screen failure is a consented participant who does not meet all the inclusion criteria, meets any of the exclusion criteria, or who has withdrawn consent prior to treatment assignment.

Screen failures may be rescreened if they qualify later and if deemed acceptable by the investigator (eg, a participant whose disease activity did not qualify at screening but later may qualify). Rescreened participants should keep the same assigned participant number for every screening/rescreening event. All procedures planned at the screening visit, including signature of a new consent form, will be performed.

5.5 Criteria for Temporarily Delaying Enrollment

Under exceptional circumstances such as delayed laboratory results, drug washout, or the impact of a pandemic, the screening period may be increased by 2 weeks, upon approval by the medical monitor.

6 STUDY INTERVENTIONS AND CONCOMITANT THERAPY

Investigational Products are all prespecified medicinal products intended to be administered to the study participants during the study conduct (ie, daxdilimab and placebo).

6.1 Study Interventions Administered

[redacted]

The placebo is supplied as a 2R vial with nominal [redacted] mL of [redacted] mM [redacted] mM [redacted] (w/v) [redacted] pH [redacted].

Both IPs are to be administered by SC injection Q4W from Day 1 to Week 20. To maintain the same number and volume of injections across all groups, the required dose will be administered as 2 injections of 1.5 mL.

The administrator of IP should be experienced in performing SC injections. The skin surface of the anterolateral thigh, upper outer triceps area, upper buttocks, or abdomen (avoiding a 2-inch [5 cm] radius around the umbilicus) should be prepared with an alcohol wipe and allowed to air dry. The skin will be pinched to isolate SC tissue from the muscle. The needle will be inserted at a 90-degree angle to the skin surface approximately halfway into the SC tissue. The IP will be slowly injected (at least 5 second duration is recommended per 1.5 mL syringe) into the SC tissue using gentle pressure. The area should not be massaged after injection. The SC injection site can be changed during the study as per participant preference. After the administration of IP, all participants will be observed for 20 minutes, except on Day 1 and Week 4 when they will be observed for at least 60 minutes.

For further information on the administration of IP, see the pharmacy manual.

Further details regarding the IPs can be found in Table 3.

Table 3 Study Interventions Administered

Intervention Label	Compound	Placebo
Intervention Name	Daxdilimab	Placebo
Intervention Description	[redacted]	
Type	Drug	Placebo
Dose Formulation	2R vial	2R vial
Unit Dose Strength(s)	100 mg/mL daxdilimab	Placebo
Dosage Level(s)	300 mg as 2 x 1.5 mL Q4W	2 x 1.5 mL Q4W
Route of Administration	SC injection	SC injection
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Sourcing	Horizon Therapeutics	Horizon Therapeutics
Packaging and Labeling	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.
Current/ Former Name(s) or Alias(es)	Current: HZN-7734 Former names: MEDI7734 and VIB7734 Alias: Daxdilimab	Not applicable

2R = 2 mL injection vial; [redacted]; IMP = investigational medicinal product; IP = investigational product; NIMP/AxMP = not an IMP; Q4W = once every 4 weeks; SC = subcutaneous

Table 4 shows the study groups according to IP.

Table 4 Study Groups

Group	Group type	IP	Dose up to Week 20	Intervention form and frequency
1 DM	Placebo / Experimental	Placebo / Daxdilimab	0 mg (no drug)	2 x 1.5 mL SC injections Q4W
2 DM	Experimental	Daxdilimab	300 mg	2 x 1.5 mL SC injections Q4W
3 ASIM	Placebo / Experimental	Placebo / Daxdilimab	0 mg (no drug)	2 x 1.5 mL SC injections Q4W
4 ASIM	Experimental	Daxdilimab	300 mg	2 x 1.5 mL SC injections Q4W

6.2 Preparation, Handling, Storage, and Accountability

- The IP vials must be refrigerated at 2-8°C (36-46°F) until the day of use.
- The investigator or designee must confirm appropriate conditions (eg, temperature) have been maintained during transit for all IPs received, and any discrepancies are reported and resolved before use of IP.

- Only participants enrolled in the study may receive IP, and only authorized site staff may supply, prepare, or administer IP.
- All IPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The unblinded pharmacist/IP Manager will be responsible for the dispensation and administration of all IPs and will endeavor to ensure that there are no differences in time taken to dispense following randomization.
- The investigator is responsible for blinded oversight of IP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the preparation of IP and for the final disposition of unused IPs are provided in the pharmacy manual.

6.3 Assignment to Study Intervention

- All participants will be centrally assigned to randomized IP using an interactive voice/web response system (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the login information and directions for the IWRS will be provided to each site.
- The IP will be dispensed at the study visits as summarized in the SoA (Section 1.3).
- Returned IPs should not be redispensed to the participants.

6.4 Blinding

- Participants will be randomly assigned in a 1:1 ratio to receive daxdilimab 300 mg or placebo at Day 1.
- Up to Week 24, the study will be double-blinded, which means that participants, investigators, and site personnel will be unaware of the IP given to the participant.
  - To reduce the risk of unblinding to the study personnel who will be evaluating the participant during the RCP of the study (from Day 1 to Week 24), an otherwise uninvolved, unblinded third party (eg, a pharmacist/IP Manager or study-site staff member) will be responsible for the dispensation and administration of all IPs and will endeavor to ensure that there are no differences in time taken to dispense following Randomization.
  - This third party will instruct the participant to avoid discussing the dosing or packaging of IP with the investigator.
  - In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded IP records at the site(s) to verify that randomization/dispensing has been conducted accurately.
  - In the event of unblinding, the instructions in the interactive response technology (IRT) manual will apply.
- At Week 24, the OLE period of the study will begin. Participants in the placebo groups (Groups 1 and 3) will be moved to a dose of 300 mg of daxdilimab. Participants initially randomized to the daxdilimab 300 mg groups (Groups 2 and 4) will remain on the same dose for the rest of the study.

  - Although all participants who have received dosing past the Week 20 visit received active treatment from Week 24, the blind for previous treatment (prior to Week 24) will remain in force until appropriate data analysis is completed.

- The investigator is responsible for all medical decisions and for the safety of the participant and is not required to consult the sponsor for unblinding.

6.5 Study Intervention Compliance

Participants will receive the IP directly from a pharmacist/IP Manager. The date and time of each dose administered in the clinic will be recorded in the source documents. The study participant identification will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the IP.

In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

6.6 Dose Modification

Modification or reduction of individual participant's dose of IP will not apply during this study.

6.7 Continued Access to IP after the End of the Study

Sponsor will not continue provision of investigational product for subjects after their study participation ends unless it is a legal requirement.

6.8 Treatment of Overdose

For this study, any dose of daxdilimab greater than the dose indicated per protocol for a given participant will be considered an overdose. Study intervention compliance (Section 6.5) should be reviewed to detect potential instances of overdose (intentional or accidental).

In the event of an overdose, the investigator should:

- Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether the IP should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
- All AEs associated with an overdose should be entered on the AE electronic case report form (eCRF) and reported using the procedures detailed in Section 8.4.4, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the SAEs reporting procedures and in an expedited manner but should be noted as nonserious on the form and the Adverse Event eCRF.
- Document the quantity of the excess dose as well as the duration of the overdose on the source document and eCRF.

The sponsor does not recommend specific treatment for an overdose.

6.9 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or topical skin treatment that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

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

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1 Permitted Therapy

Participants are allowed to be on permitted standard of care medication (Table 5) if stable prior to Screening:

- Azathioprine, Tacrolimus, Ciclosporin, Hydroxychloroquine, and Mycophenolate Mofetil must be at a stable dosage for at least 4 weeks prior to Screening and through study.
- Methotrexate (oral or SC) at stable dosage and route of administration for at least 4 weeks prior to Screening and through study.
- Corticosteroids at stable dose up to 20 mg/day prednisone equivalent for at least 4 weeks prior to Screening. Investigators will taper prednisone (Section 8.2.4) from Weeks 4 to 20 and during OLE if participants are stable or improving.

If participants fail to respond to the medication, do not tolerate it, and/or decide to stop taking it, they should discontinue it according to the washout period prior to the first administration of IP at Day 1 visit (Table 5) and through the last study visit.

Table 5 Permitted Standard of Care Medication

Drug	Washout period prior to first dose (Day 1)	Maximally allowed stable dose
Corticosteroids	4 weeks	20 mg/day
Methotrexate	4 weeks	25 mg/week
Azathioprine	8 weeks	3 mg/kg
Ciclosporin	8 weeks	3 mg/kg
Hydroxychloroquine	8 weeks	400 mg daily
Mycophenolate Mofetil	8 weeks	3000 mg daily
Tacrolimus	8 weeks	3 mg/kg

6.9.2 Prohibited Therapy

Participants who, during the study, start prohibited medications or new therapies that have been demonstrated to be effective for treatment of DM or ASIM (except those allowed as concomitant medication [Section 6.9.1]) will be withdrawn from IP.

Participants who start prohibited medications or therapies for other reasons during the study may be withdrawn from study treatment if an impact on efficacy assessment or safety of the participants is expected. If in any doubt, investigators are advised to discuss medications with the medical monitor.

Table 6 lists prohibited medications that are not to be used from the defined washout periods before the first administration of IP at the Day 1 visit through the last study visit.

Table 6 Prohibited Therapy

Prohibited therapies	**Washout period prior to first dose (Day 1)**
Oral steroids > 20 mg/day, and any IM and IV steroids	4 weeks
IA steroids [a]	4 weeks
Medium to high potency topical steroids	2 weeks
Plasma exchange	8 weeks
Tofacitinib, IVIG [b]	4 weeks
Leflunomide or cyclophosphamide	3 months
Rituximab	3 month and detectable B-cells
Infliximab, adalimumab, golimumab, certolizumab	8 weeks
Etanercept	1 month
Anakinra	1 week
Non-biologic immunomodulatory or immunosuppressive agents that are not permitted therapy (eg, dapsone, danazol, sulfasalazine, mizoribine, mechanistic target of rapamycin inhibitors, retinoids, thalidomide, lenalidomide, adrenocorticotropic hormone analogs, dehydroepiandrosterone), or JAK inhibitors	4 weeks
B-cell targeting or depleting therapy	3 months and detectable B-cells
Anti-BDCA2 (BIIB059)	6 months
Daxdilimab	Lifetime
Any biologic or antiproliferative agents	4 weeks or 5 half-lives, whichever is longer
Experimental drugs	30 days, 5 half-lives, or twice the duration of the biological effect of the agent, whichever is longer.
Live-attenuated vaccine	4 weeks

BDCA2 = blood dendritic cell antigen 2; JAK = Janus kinase; IA = intra-articular; IG = immunoglobulin; IM = intramuscular; IV = intravenous; IVIG = intravenous immunoglobulin.

a Prohibited during the first 24 weeks, after which it should be discussed with the medical monitor.

b The use of other therapeutic IGs should be discussed with the medical monitor before use.

6.9.3 Rescue Therapy

Rescue therapy is any new background therapy or increase in dose above baseline dose of any permitted therapy given to participants.

For some rescue medications, IP may be continued after discussion with and approval by the medical monitor. However, if participants receive a prohibited medication as a rescue (Section 6.9.2), they should be discontinued from IP, but stay in the study for safety assessments.

Rescue medication for worsening DM or ASIM should be administered at the discretion of the investigators as clinically indicated. Rescue medications are not supplied by the sponsor and should be supplied through normal clinical pathways.

The use of rescue medications is allowable for clinical deterioration and should be administered at the discretion of the investigator and without prior contact with the medical monitor or sponsor.

Participants who receive rescue therapy will be considered treatment failures for subsequent endpoints.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

7 DISCONTINUATION OF IP AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of IP

The IP must be permanently discontinued if the Investigator determines that continuing it would result in a significant safety risk for that participant and for the additional reasons described below:

- Withdrawal of consent for continued study participation
- Withdrawal of consent for further treatment with IP
- Receipt of prohibited medications that require discontinuation of IP
- Pregnancy, lactation, or a decision to become pregnant
- Any SAE that is considered to be related to IP by the Investigator, the Sponsor, or the SDMC
- Any liver safety related events (Section 10.4)
- Anaphylaxis or a CTCAE Grade 4 hypersensitivity reaction that is considered to be related to IP the Investigator, the Sponsor, or the SDMC
- Any CTCAE grade 3 opportunistic infection (see Section 10.6) that is considered to be related to IP the Investigator, the Sponsor, or the SDMC
- Hematologic Malignancy
- An AE that, in the opinion of the Investigator, the SDMC, and/or the Sponsor, warrants discontinuation of further dosing.
- Any other reason when the Investigator determines that continuing IP would result in a significant safety risk for that participant.

In addition, the study has a Safety Data Monitoring Committee to provide safety signal detection through the study and make recommendations for study stopping if any safety concerns are identified (see section 10.1.7)

If IP is permanently discontinued, the participant should, if at all possible, remain in the study and complete all remaining study visits/assessments (without administration of IP), provided such continued participation will not detrimentally affect the health, and safety, and welfare of the participants per investigator determination.

- Participants who prematurely discontinue IP prior to Week 24 will be followed according to the regularly scheduled evaluations until Week 24 and at least 12 weeks after the last administration of IP, whichever is longer, unless they withdraw consent from study participation (Section 7.2) or are lost to follow-up (Section 7.3).
- Participants who have progressed past Week 20 will discontinue treatment and complete the end of treatment visit 4 weeks after their last dose followed by 8 weeks of safety follow-up.

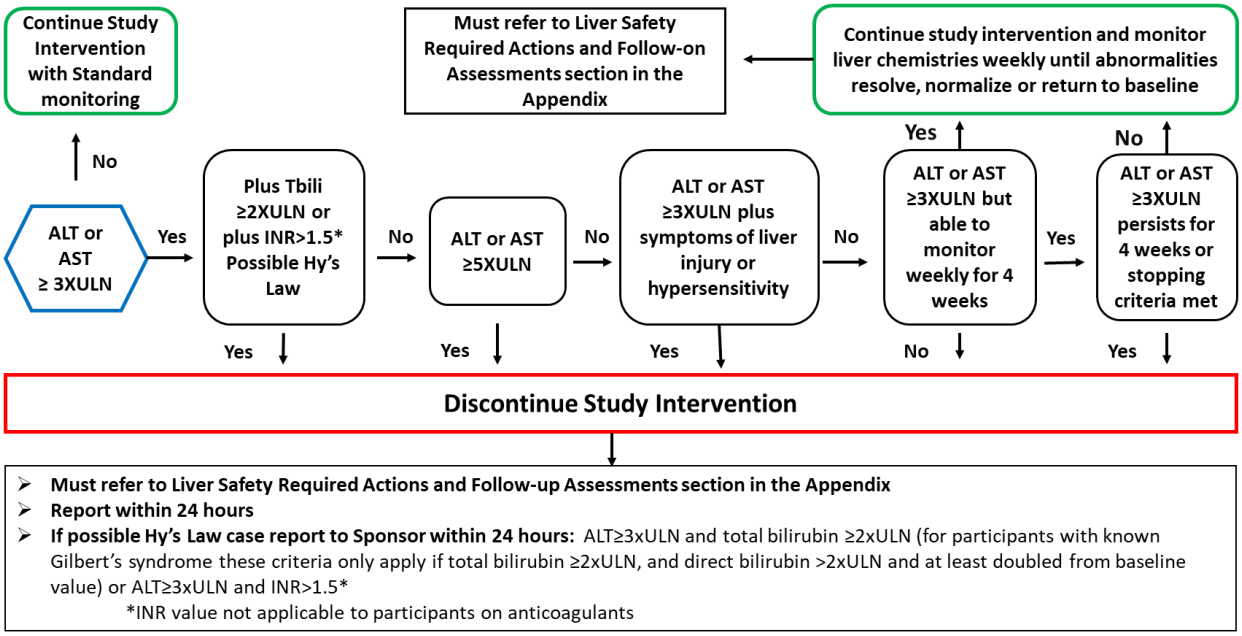
Participants will not be automatically removed from the study if any administration of IP is missed.

See the SoA (Section 1.3) for data to be collected at time of discontinuation of IP and other scheduled evaluations.

7.1.1 Liver Chemistry Stopping Criteria

Discontinuation of IP for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in Figure 2 or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

Figure 2 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



ALT = alanine transaminase; AST = aspartate transaminase, INR = international normalized ratio; IP = investigational product; Tbili = total bilirubin, ULN = upper limit of normal.
Note: study intervention refers to IP

Appendix 4: Liver Safety Guidelines includes liver safety suggested actions and follow-up assessments, and the criteria to continue study intervention with standard monitoring.

7.1.2 QTc Stopping Criteria

If a clinically meaningful finding is identified (including, but not limited to, changes from baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the investigator or qualified designee will determine if the participant can continue IP and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

A participant who meets the following criteria based on single ECG readings will be withdrawn from IP:

- QTc > 500 msec OR Uncorrected QT > 600 msec

For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	Discontinuation QTc Threshold with Bundle Branch Block
< 450 msec	> 500 msec
450 to 480 msec	≥ 530 msec

7.1.3 Temporary Discontinuation

The decision on how to proceed if a participant needs, for any reason, to stop taking the IP, will be made on a case-by-case basis after evaluation by the investigator and the medical monitor. It will be at the discretion of the investigator and the medical monitor whether the participant should restart IP after temporary discontinuation.

7.1.4 Restart/Rechallenge

Restart or rechallenge of the IP is not allowed in the following situations:

- Liver chemistry stopping criteria are met by any participant
- Any CTCAE Grade 3 or higher allergic reaction considered to be related to the IP
- Any CTCAE Grade 3 or higher infections considered to be related to the IP

7.2 Participant Early Withdrawal from the Study

Participants are free at any time to withdraw from the study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such participants will always be asked about the reason(s) for withdrawal and the presence of any AEs. AEs will be followed-up.

Additionally, a participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

Participants who withdraw should perform an End of Study/Early Termination Visit as shown in the SoA (Section 1.3), if consent for this visit is not also withdrawn. If a participant withdraws consent to participation in the study, then no further study visits or data collection should take place.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The primary reason for participant withdrawal from the study should be recorded on the eCRF using one of the following categories:

- Lost to Follow-up – the participant does not return to the clinic for scheduled assessments and does not respond to the site's attempts to contact the participant;
- Withdrawal by Participant/Guardian – the participant wishes to withdraw from the study. The clinical site should attempt to determine the underlying reason for the voluntary withdrawal and document it on the eCRF;

- Study terminated by Sponsor – the Sponsor, IRB, or regulatory agency terminates the study; or
- Death

7.3 Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, by telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered lost to follow-up.

7.4 Replacement

No replacement is planned in this study.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.
- Safety, laboratory, and/or analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel.
- Instructions for the collection, processing, storage, and shipment of biological samples will be detailed in a separate laboratory manual provided to the sites.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General/Baseline Procedures

The following procedures will be performed once at the beginning of the study:

1. Signing of ICF
2. Medical history
   - Medical history information to be collected includes all ongoing conditions and relevant/significant medical history (including all major hospitalizations and surgeries), as determined by the investigator.
3. Review of inclusion and exclusion criteria
4. Collection of demographic data
   - Demographic information to be collected includes year of birth, sex, race, and ethnicity.
5. Height measurement
6. Review of participant eligibility

8.2 Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

Efficacy will be assessed with:

- Total improvement score (TIS) based on the 6 CSM:
  [redacted]
  3. Physician global disease activity (PhGDA) (part of the [redacted]
  4. Manual muscle testing 8 (MMT8) bilateral
  5. Laboratory muscle enzymes
  6. Extramuscular global assessment (part of the [redacted]
- Cutaneous dermatomyositis disease area and severity index (CDASI)
- Steroid taper
- [redacted]

8.2.1 TIS Based on the 6 CSM

The TIS is derived from standardized clinical response criteria that are recommended for use as primary endpoint in myositis therapeutic. The criteria use the 6 CSM, combining the absolute percentage change in each with varying weights to obtain a TIS on a scale of 0-100. Different thresholds of improvement have been set for minimal, moderate, and major response. The criteria may be used as a continuous outcome measure, using the TIS, or as a categorical outcome of improvement (minimal, moderate, or major improvement) and thus are a hybrid measure. Improvement category thresholds for minimal, moderate, and major improvement have been developed and validated for DM and PM. (Find online calculator in MRC 2016.)

[redacted]

[redacted]

8.2.1.3 PhGDA (Part of [redacted]

The PhGDA is the physician's judgment of overall disease activity (extramuscular organ systems plus muscle disease activity) based on all clinical laboratory assessments. It uses a 10 cm VAS that ranges from "no evidence of disease activity" to "extreme or maximum disease activity" and a 5 point Likert scale that ranges from 0 (none activity) to 4 (extremely severe activity). (Find online form in PhGDA Form 02.)

Participants will be considered to have complete response if, during the study, they have no evidence of disease activity (ie, PhGDA VAS = 0) while on therapy.

8.2.1.4 MMT8 Bilateral

The MMT8 bilateral is a set of 8 designated muscles tested bilaterally (potential score 0-140). Axial (neck flexors) testing is included, so that potential MMT8 score is 150. (Find online form in MMT8 2007.)

8.2.1.5 Laboratory Muscle Enzymes

The levels of creatine kinase, the transaminases (alanine transaminase [ALT] and aspartate transaminase [AST]), lactate dehydrogenase, and aldolase will be measured to evaluate the effect of daxdilimab in muscle-associated enzymes.

8.2.1.6 Extramuscular Global Assessment (part of [redacted])

The extramuscular global assessment provides an overall evaluation for the disease activity in all extramuscular systems (excluding muscle disease activity) using a 10 cm VAS that ranges from "no evidence of disease activity" to "extreme or maximum disease activity". (Find online form in [redacted]

[redacted]

8.2.3 CDASI

The CDASI (V 2.0) is an outcome measure used to assess the severity of cutaneous DM and detect improvement in disease activity. The scale rates disease involvement in 15 different body areas using 3 activity (erythema, scale, erosion/ulceration) and 2 damage (poikiloderma, calcinosis) measures. The presence and severity of Gottron's papules on the hands, periungual

changes and alopecia are also captured. The activity score ranges from 0 to 100 and the damage score from 0 to 32. Higher scores indicate greater disease severity.

8.2.4 Steroid Taper

For participants taking corticosteroid (prednisone or equivalent) and who are stable or improving, investigators will taper their dose 2.5 mg/day (prednisone equivalent) every 4 weeks from Week 4 through Week 20 (Table 7). Note that is not permitted to change the corticosteroid dose between Weeks 20 and 24 (Figure 1).



If symptoms worsen, participants should call the investigator for instructions (eg, hold at current dose or step back up to previous dose).

Criteria for Worsening and Holding Steroid Taper

If participants are not stable or improving and criteria for worsening (see below) are met, steroid taper will be held.

Steroid taper will be held if the PhGDA has a global worsening from Baseline by ≥ 2 cm on the 10 cm VAS **and** at least one of the following occurs:

- Worsening by ≥ 20% from Baseline on the MMT8 score **or**
- Worsening of the extramuscular global activity by ≥ 2 cm from Baseline on the [redacted] VAS **or**
- Worsening of any 3 of the CSMs by ≥ 30% from Baseline

Criteria for Confirmed Worsening and Designating Treatment Unsuccessful, and Offering Alternative Therapy or Steroid Burst

The treatment will be considered unsuccessful, and the participant offered an alternative therapy or the steroid taper burst, if on 2 consecutive visits the PhGDA has a global worsening by ≥ 2 cm from Baseline on the 10 cm VAS **and** at least one of the following occurs (also on 2 consecutive visits):

- Worsening by ≥ 20% from Baseline on the MMT8 score on 2 consecutive visits **or**
- Worsening of the extramuscular global activity by ≥ 2 cm from Baseline on the [redacted] VAS on 2 consecutive visits **or**

- Worsening of any 3 of the CSM by ≥ 30% from Baseline on 2 consecutive visits

The investigator should complete the assessments in Section 1.3 on clinic visit days and confirm the scales once the enzyme results from the central laboratory are available. Based on this reassessment, the participant may be called to change the steroid taper instructions.

[redacted]



8.3 Safety Assessments

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

Safety will be assessed by:

- Measurement of physical examinations
- Monitoring of vital signs
- Electrocardiograms (ECGs)
- Monitoring of hematology, blood chemistry, and urinalysis
- Pregnancy testing
- Assessment of local injection tolerability
- Monitoring and recording of all AEs

8.3.1 Physical Examinations

- A complete physical examination will include assessment of head, ears, eyes, nose, throat, lungs, heart, abdomen, skin, and extremities.
- Height and weight will be measured and recorded at Screening, but only weight will be measured during Treatment and SFU.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses. Any clinically meaningful change from the screening physical exam should be recorded as an AE or SAE.

8.3.2 Vital Signs

- Vital signs will be measured before blood collection in a seated position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.
- One reading of blood pressure and pulse will be taken.

8.3.3 Electrocardiograms

- Single 12-lead ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTc intervals. Section 7.1.2 describe the criteria for QTc withdrawal and any additional QTc readings that may be necessary.
- The ECGs should be performed after 10 minutes rest in supine position and after vital signs are collected.
- Clinically meaningful findings in the ECG should exclude a participant from study participation (as deemed appropriate by the investigator). Any clinically meaningful value will be reported as an AE.

8.3.4 Clinical Safety Laboratory Tests

- Laboratory tests will include urinalysis, hematology with differential, a standard chemistry panel (chemistry includes liver function tests), and a serum pregnancy test at Screening for WOCBP.
- All protocol-required laboratory tests must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- The investigator must review the laboratory results, document this review, and record any clinically meaningful changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically meaningful unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically meaningful by the investigator or medical monitor.
  - If clinically meaningful values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
  - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically meaningful by the investigator (eg, SAE or AE or dose modification), then the results must be recorded.
- Except for the highly sensitive urine pregnancy test, which will be performed by study staff at the clinic, all the tests detailed in Table 8 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 8 Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters
Hematology	• Platelet count • Red blood cell (RBC) count • RBC indices: – Mean corpuscular volume (MCV) – Mean corpuscular hemoglobin (MCH) – %Reticulocytes • White blood cell (WBC) count with differential: – Neutrophils – Lymphocytes – Monocytes – Eosinophils – Basophils • Hemoglobin • Hematocrit
Routine chemistry [a]	• Blood urea nitrogen (BUN) • Potassium • Creatinine • Sodium • Calcium • Glucose (nonfasting) • Hemoglobin A1C (HgA1C) • Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) • Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) • Alkaline phosphatase (ALP) [b] • Total and direct bilirubin • Total protein
Urinalysis [c]	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)
Muscle enzymes	• Aldolase • Creatine kinase • ALT • AST • Lactate dehydrogenase (LDH)
Pregnancy testing	• Highly sensitive urine pregnancy test [d] • Highly sensitive serum β-human chorionic gonadotropin (βhCG) pregnancy test [d]
Other screening tests	• Tuberculosis (TB) test (QuantiFERON-TB Gold Plus or T SPOT) [e] • Follicle stimulating hormone (FSH) and estradiol [f] • Serology: o Human immunodeficiency virus (HIV) antibody

Table 8 Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters
	• Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), and hepatitis C virus antibody (HCVAb) [g, h] • Anti Jo-1 antibody • All study-required laboratory tests will be performed by a central laboratory except for the highly sensitive urine pregnancy test, which will be performed by study staff at the clinic.

a Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.1 and Appendix 4: Liver Safety Guidelines. All events of ALT or AST ≥ 3 × upper limit of normal (ULN) and total bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT or AST ≥ 3 × ULN and international normalized ratio (INR) > 1.5 (if INR measured), which may indicate severe liver injury (possible Hy's law), must be reported to sponsor in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
b If alkaline phosphatase is elevated, consider fractionating.
c Urine collection can be postponed for up to 14 days in women with menstrual bleeding or a urinary tract infection at the scheduled visit.
d As needed in women of childbearing potential or women who are postmenopausal for less than 2 years prior to Screening, have nontherapy-induced amenorrhea for less than 12 months prior to Screening, or are not surgically sterile (absence of fallopian tubes, ovaries and/or uterus). Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.
e The results of an interferon-γ (IFN-γ) release assay (ie, QuantiFERON-TB Gold Plus or T-SPOT) performed within 12 weeks of the Screening visit (if available) are acceptable, provided there is no reason to suspect any re-exposure.
f As needed in women of nonchildbearing potential only. These tests do not have to be repeated if performed within 12 weeks prior to Screening (eg, Rescreening).
g Serum virology does not have to be repeated if performed within 12 weeks prior to Screening (eg, Rescreening).
h In the cases of positive test results, additional reflex testing will be performed.

8.3.5 Pregnancy Testing

- A serum β-human chorionic gonadotropin (βhCG) pregnancy test will be performed to all WOCBP by a central laboratory at Screening.
- A urine pregnancy test will be performed by study staff at the clinic and prior to the administration of IP from Day 1 through Week 24 and at the End of Study visit.

8.3.6 Local Injection Tolerability Assessments

Local injection tolerability assessments will be performed approximately 30 minutes postdose (can be performed any time at non-dosing visits.

The investigator, or designee, will evaluate the injection sites at these visits, document the presence or absence of local intolerance/injection site reactions, and will open an AE in case of local injection site intolerance. Additional follow-up after the last treatment visit can be performed for any ongoing injection site reactions.

8.4 AEs, SAEs, and Other Safety Reporting

The definitions of AEs, SAEs, and unsolicited and solicited AEs can be found in Appendix 2: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following them up (Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative [LAR]).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs, SAEs, and adverse events of special interest (AESIs) will be collected from the signing of the ICF at the timepoints specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 2: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the IP or study participation, the investigator must promptly notify the sponsor.

8.4.2 Method of Detecting AEs and SAEs

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

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AESIs (as defined in Section 8.4.6) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Final AEs, SAEs, and AESIs follow-up will occur at the participant's scheduled visit approximately 12 weeks after the last administration of IP. Further information on follow-up procedures is provided in Appendix 2: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of an IP under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IP under clinical investigation. The

sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.5 Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until 6 months following the last dose of IP and, if indicated, in female partners of male participants will be collected until 3 months following the last dose of IP.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant or female partner of male participant pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the sponsor. Additional follow-up after delivery will also be collected for abnormalities and/or developmental issues.
- Any poststudy pregnancy-related SAE considered reasonably related to the IP by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue IP but will not be withdrawn from the study.

8.4.6 Adverse Events of Special Interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication (within 24 hours) by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. AESIs may be added or removed during a study by protocol amendment.

The following AESIs are identified for this study:

- Hypersensitivity reaction, including anaphylaxis (Appendix 5: National Institute of Allergy and Infectious Disease and Food and Allergy Anaphylaxis Network Guidance for Anaphylaxis Diagnosis)
- Herpes zoster infection
- Severe viral infection/reactivation (CTCAE Grade 3 or higher) (Appendix 2; Section 10.2.3)
- Opportunistic infection (Appendix 6: Opportunistic Infections)
- Malignancy (except non-melanoma skin cancer)

8.5 Pharmacokinetics

Serum samples of approximately 3.5 mL (whole blood collection tube) will be collected for measurement of serum concentrations of daxdilimab at the visits and timepoints specified in the SoA (Section 1.3).

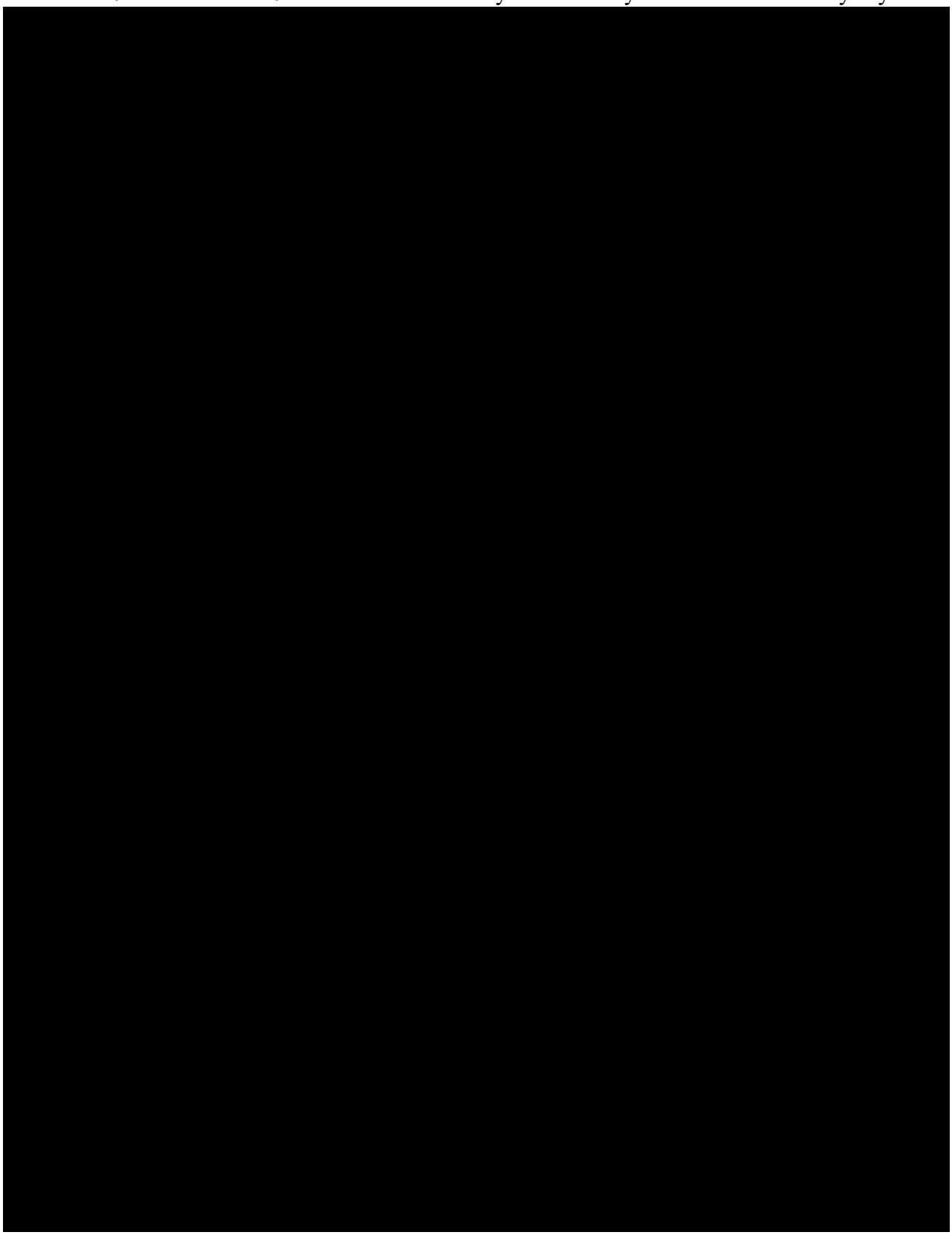
Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the sponsor.

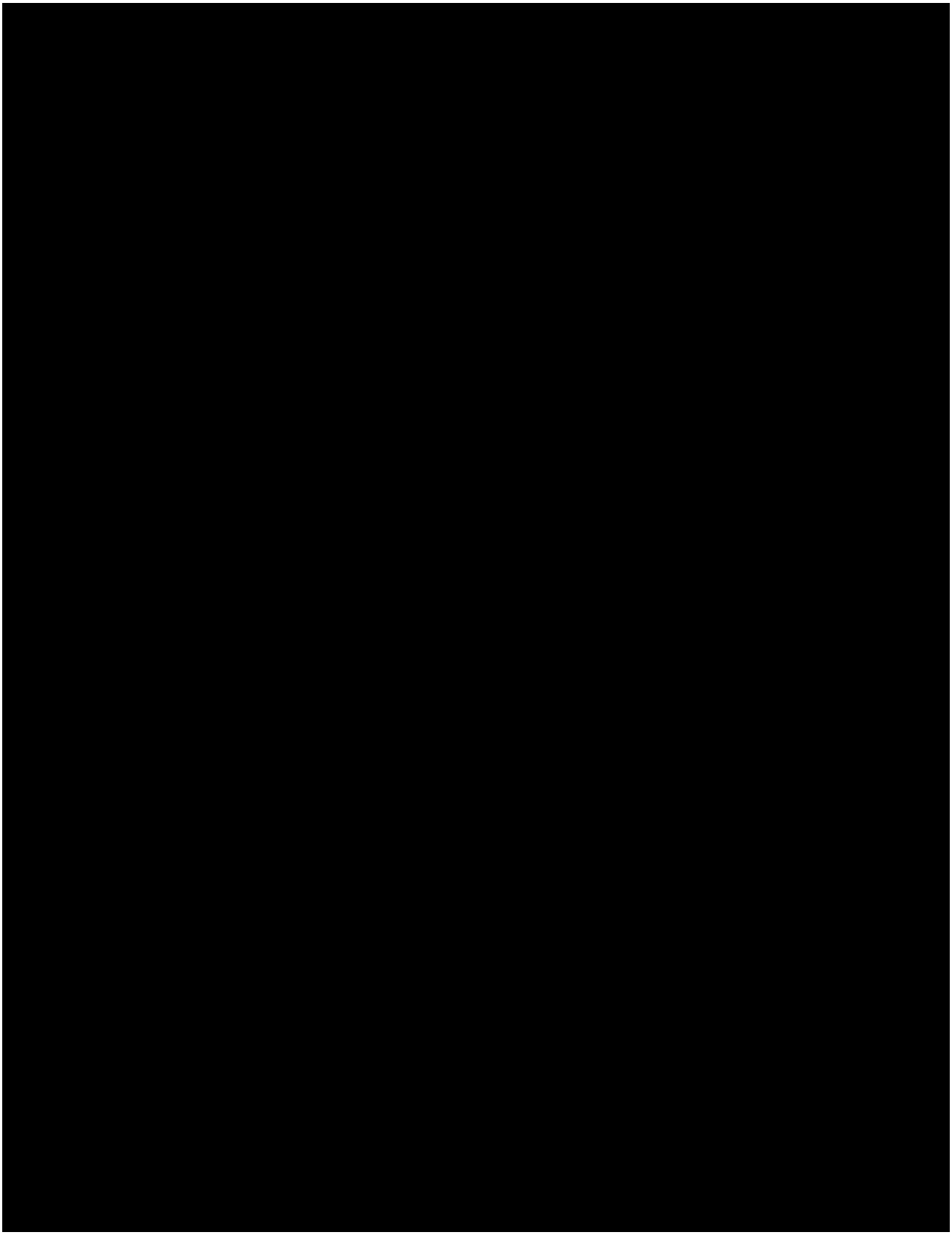
Instructions for the collection, processing, handling, storage, and shipping of biological samples will be provided by the sponsor in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded in the eCRF.

Samples collected for analyses of daxdilimab serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Intervention concentration information that would unblind the study will not be reported to investigative sites or blinded personnel.







[redacted]

8.9 Immunogenicity Assessments

Antibodies to daxdilimab will be assessed by the incidence and titer of ADAs in serum samples collected from all participants according to the SoA (Section 1.3).

Additionally, serum samples should also be collected at the final visit from participants who discontinued IP or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to daxdilimab, and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to daxdilimab and/or further characterize the immunogenicity of daxdilimab.

The detection and characterization of antibodies to daxdilimab will be performed using a validated assay method by or under the supervision of the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of daxdilimab.

Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to daxdilimab.

8.10 Quality of Life

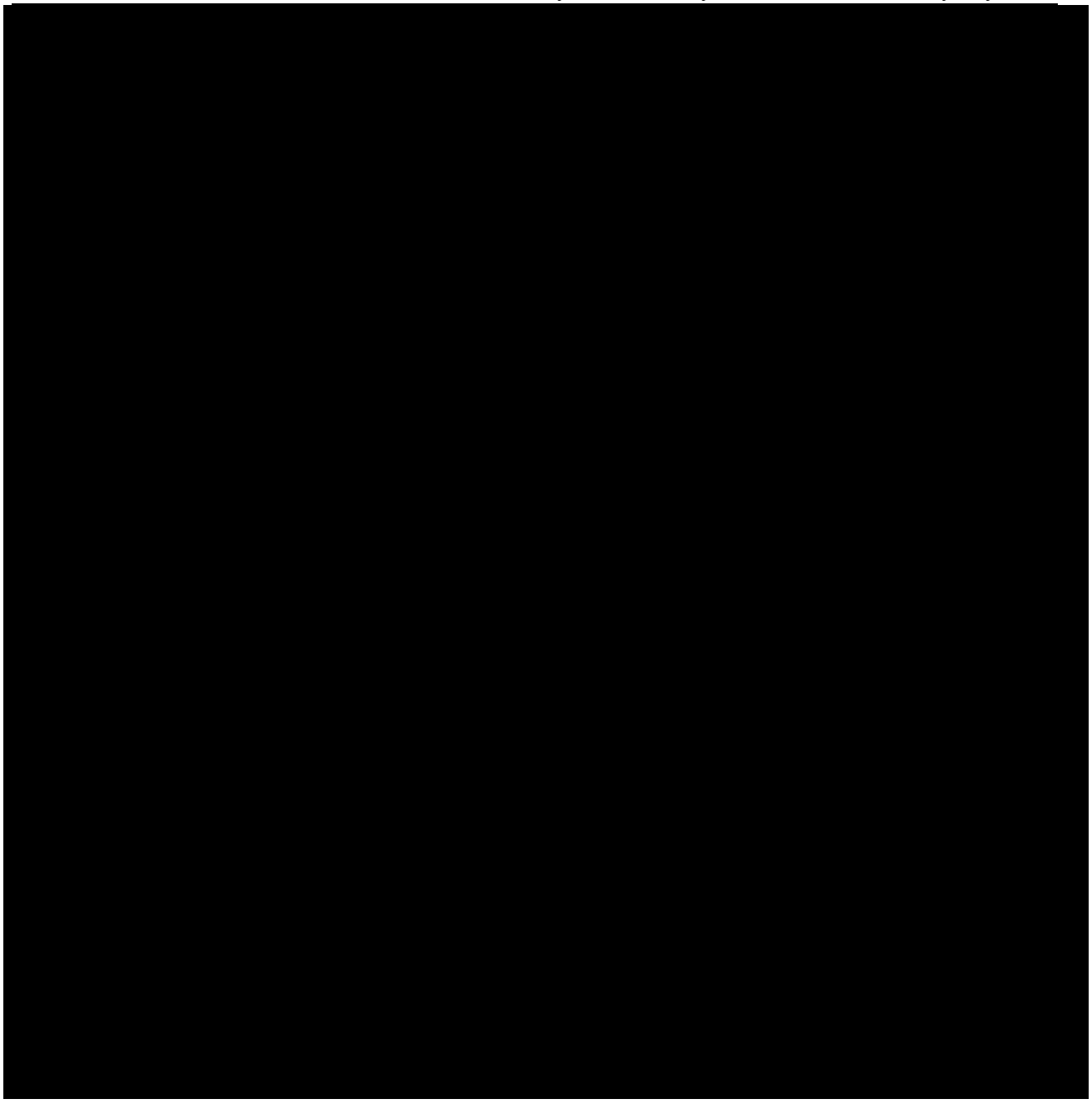
Planned timepoints for all quality of life assessments are provided in the SoA (Section 1.3).

Quality of life will be assessed with:

- [redacted]

[redacted]

[redacted]



9 STATISTICAL CONSIDERATIONS

This section is a summary of the planned statistical analyses. A comprehensive statistical analysis plan (SAP) will be prepared. Any deviations from this plan will be reported in the CSR.

9.1 Statistical Hypotheses

Not applicable.

9.2 Analysis Sets

Full Analysis Set: The Full Analysis Set will include all randomized participants who receive any dose of IP in the study. Participants will be analyzed according to the treatment randomized. The efficacy analysis will be based on the Full Analysis Set.

Safety Analysis Set: The Safety Analysis Set will include all participants who received any dose of IP in the study. Participants will be analyzed according to the treatment that they actually received. Safety, ADA, and [redacted] analyses will be based on Safety Analysis Set.

PK Analysis Set: The PK Analysis Set will include all participants who receive any dose of daxdilimab in the study and have at least one quantifiable serum PK observation post first dose. Participants will be analyzed according to the treatment that they actually received. The PK analysis will be based on the PK Analysis Set.

9.3 Statistical Analyses

9.3.1 General Considerations

Tabular summaries will be presented by treatment group. For continuous data, number of participants, mean, standard deviation, median, minimum, and maximum will be reported. For categorical data, percent and frequency will be reported. Data listings will be sorted by treatment group and participant number.

9.3.2 Primary Efficacy Endpoint Analyses

Within each of the DM and ASIM populations, the primary endpoint of TIS at Week 24 will be summarized descriptively based on the observed data using the Full Analysis Set.

9.3.3 Secondary Efficacy Endpoint Analyses

Within each of the DM and ASIM populations, the secondary efficacy endpoints will be summarized descriptively based on the observed data using the Full Analysis Set.

9.3.4 Safety Analyses

The safety analyses will be based on the Safety Analysis Set. Adverse events will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). For each of the DM and ASIM populations, the number and percentage of participants reporting TEAEs will be summarized for each treatment group by MedDRA system organ class and preferred terms, by

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severity, and by relationship to IP. The number and percentage of participants reporting TESAEs and treatment-emergent AESI will also be summarized for each of the DM and ASIM populations.

Other safety parameters, including but not limiting to laboratory assessments, vital signs, and ECG will also be summarized for each of the DM and ASIM populations as appropriate.

9.3.5 Pharmacokinetics Analyses

The PK analysis will be based on the PK Analysis Set. Descriptive statistics of the serum daxdilimab concentration will be tabulated by visit and by treatment group for each of the DM and ASIM populations. Exposure-response ([redacted] ADA, safety, and efficacy) analysis may be conducted using serum daxdilimab concentration and available drug response data per the sponsor's discretion and as the data will allow.

[redacted]

9.3.7 Immunogenicity Analyses

Number and percentage of participants who develop positive ADA as well as the titer of positive ADA will be summarized by treatment group and by visit for each of the DM and ASIM populations using the Safety Analysis Set.

9.3.8 Exploratory Analyses

The exploratory endpoints analyses will be detailed in the SAP.

9.4 Planned Analysis

9.4.1 Final Analysis

The final analysis will be conducted separately for each of the DM and ASIM populations after the last participant has completed the study or discontinued early from study for that population.

[redacted]

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
  - Applicable ICH Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and after completion of the study for whatever period is required, per regulations.

10.1.3 Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant or their LAR and answer all questions regarding the study.
- Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate.
- Potential participants must be informed that their participation is voluntary and that they may withdraw from the study at any time for any reason, without prejudice. They or their LARs will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative.
- If new safety information results in significant changes in the risk/benefit assessment, or if any new information becomes available that may affect the willingness of a participant to continue to participate, the consent form should, if necessary, be reviewed and updated by the IRB/Research Ethics Board (REB). All participants (including those already being treated) should be informed of the new information, given a copy of the revised form, and asked to give their consent to continue in the study.
- Participants who are rescreened are required to sign a new ICF.

10.1.4 Biological Specimens and Data

Study data and samples are protected by the use of a participant ID number, which is a number specific to the participant. The investigator is in control of the information that is needed to connect a study sample to a participant. A participant may withdraw consent to collect samples or personal health data at any time by notifying the investigator. If consent is withdrawn, any samples collected prior to that time may still be given to and used by the sponsor, but no new personal health data or samples will be collected unless specifically required to monitor the safety of the participant. If consent is withdrawn, the sponsor is not required to destroy information or data already collected. Sponsor may store samples for up to 15 years after the end of the study to achieve study specified objectives.

10.1.4.1 Genetics

Use/Analysis of DNA

Genetic variation may impact a participant's response to IP, susceptibility to, and severity and progression of disease. Variable response to IP may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. The specifics of genetics (DNA) evaluation are found in Section 8.8. Whole genome sequencing will not be performed.

Samples of DNA will be used for research related to daxdilimab, DM, or ASIM and related diseases. They may also be used to develop tests/assays, including diagnostic tests related to daxdilimab and/or interventions of this drug class and DM or ASIM. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).

To test for polymorphisms in genes that may be related to the development of DM or ASIM or to the mechanism of action of daxdilimab (eg, Fc gamma receptor), DNA will be isolated from blood and analyzed at Baseline.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to daxdilimab or IPs of this class to understand the study disease or related conditions.

The results of genetic analyses may be reported in the CSR or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. No personal details identifying the individual will be available to sponsor or designated organizations working with the DNA. Accordingly, as the evaluation is exploratory, specific results will not be made available to the investigator, participant, or other parties. Aggregate results may be reported in the CSR or separately in a scientific report or publication.

10.1.4.2 Specimen Storage and Future Use

Once study specified objectives are completed, samples will be destroyed or with participant's consent, leftover samples may be used for future research.

It is not always possible at study start to define or predict what new research within a disease, new information related to study drug, or new analysis techniques may be generated or published. Samples stored for future use may prove beneficial to better understanding the safety aspects of drug administration or mechanism of action, or further the knowledge related to disease pathogenesis, risk factors, or how a participant may respond to study drug. This research may be undertaken by sponsor or others such as universities to contribute to the understanding of disease/drug pharmacology, or other diseases, the development of related or new treatments, or research methods.

Samples stored for future research are labeled with the same sample identification number used in the main study. If the participant withdraws consent for participating in future research, the sponsor will locate the participant's sample and destroy it, unless the sample was anonymized (information linking sample to participant was removed). However, if the participant's sample

has already been used for research, the sponsor is not required to destroy the results of this research. In this case only, the remaining sample(s) will be destroyed.

If the participant consents to have their samples used for future research, this additional research may not start immediately and may start at any time during the storage period. The participant's samples will be stored by the sponsor with similar samples in a secure laboratory. The participant's samples will not be kept for more than 15 years after the end of the study in which they were collected. If the participant chooses not to allow their study samples to be used for future research, the samples will be destroyed by the sponsor once they are no longer required for the main study.

10.1.5 Recruitment Strategy

Sites will use advertisements and patient-facing recruitment materials that are approved by the IRB/IEC and the sponsor.

10.1.6 Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/REB members, and by inspectors from regulatory authorities.

The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

Serious Breach

Suspected Serious Breaches must be reported to the study team or the Clinical Out-of-Hours Support Program: https://wwwext.amgen.com/science/clinical-trials/clinical-out-of-hours-support-program immediately and no later than 1 calendar day from the time of awareness.

A Serious Breach is a breach of any of the following:

- Good Clinical Practice (GCP)
- the clinical trial protocol
- an applicable regulation that is likely to impact to a significant degree either of the following:

- the safety, physical, or mental integrity and the rights of the subject
- the reliability and robustness of the data and the scientific value of the trial

10.1.7 Committees Structure

A contract research organization will evaluate the clinical data for study entry qualification.

An external, Safety Data Monitoring Committee (SDMC) will evaluate safety data at regular intervals throughout the study and make recommendations to the sponsor as needed. The SDMC will not perform a futility analysis or consider early study completion for efficacy.

10.1.7.1 Safety Data Monitoring Committee

Participant safety will be continuously monitored by the external, independent SDMC, which includes safety signal detection at any time during the study. The SDMC is also responsible for supporting study integrity and interpretability based on their review of ongoing study conduct.

All safety data collected will be summarized and reviewed by the SDMC for agreement of next steps. For additional details, refer to the SDMC Charter.

10.1.8 Dissemination of Clinical Study Data

Study results will be published on ClinicalTrials.Gov and Clinical Trials Information System (CTIS) within 1 year of end of study. Additionally, information may be found at clinicaltrialsregister.eu/.

10.1.9 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in eCRF Completion Guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan(s).
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be

destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.10 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source documents will consist of case and visit notes (clinical medical records) containing demographic and medical information and the results of any tests or assessments.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.11 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

For study termination:

- Discontinuation of further IP development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should assure appropriate participant therapy and/or follow-up.

10.1.12 Publication Policy

The publication policy will be addressed in the Research and Financial Agreement, and all details outlined in the agreement will apply to this protocol. The study will be registered on ClinicalTrials.Gov prior to the first participant being dosed.

10.2 Appendix 2: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of IP, whether or not considered related to the IP.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IP.

Definition of Unsolicited and Solicited AE

- An unsolicited AE is an AE that was not solicited and that is communicated by a participant/LAR(s) who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participant/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant/LAR(s) concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant/LAR(s) will be collected during an interview with the participant/LAR(s) and by review of available medical records at the next visit.
- Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned.

Events Meeting the AE Definition

- Conditions newly detected or diagnosed after the signing of the ICF, including conditions that may have been present but undetected prior to the start of the study
- Conditions known to have been present prior to the start of the study that worsen after the signing of the ICF
- Signs, symptoms, or the clinical sequelae of a suspected drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either IP or a concomitant medication (overdose per se should not be reported as an AE)
- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically meaningful in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition)
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However,

the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events not Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.2.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

- Results in death
- Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, consult the Sponsor's Medical Monitor.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Other situations:
  - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse. If in doubt as to whether or not an event qualifies as an important medical event, consult the Sponsor's Medical Monitor.

10.2.3 Document and Follow-Up of AE and/or SAE

AE and SAE Document

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

Assessment of Intensity

- Severity will be graded according to the CTCAE, version 5.0. The determination of severity for events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to Grade 5 as defined below:
  - Grade 1 (mild): An event of mild intensity that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

- Grade 2 (moderate): An event of moderate intensity that is usually alleviated with additional, specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the participant.
- Grade 3 (severe): A severe event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the participant.
- Grade 4 (life-threatening): An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the participant to perform activities of daily living (eating, ambulation, toileting, etc).
- Grade 5 (fatal): Death (loss of life) as a result of an event.

Assessment of Causality

- The investigator is obligated to assess the relationship between IP and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IP administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor (Horizon Therapeutics). However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor (Horizon Therapeutics).
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor (Horizon Therapeutics) to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- Upon request, if a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor (Horizon Therapeutics) with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.

- The investigator will submit any updated SAE data to the sponsor (Horizon Therapeutics) within 24 hours of receipt of the information.

10.2.4 Reporting of SAEs

Any death, life-threatening event, or other SAE experienced by a participant during the course of the study, whether or not judged drug-related, must be reported within 24 hours of knowledge of the event by entering the information into the eCRF. If unable to access the eCRF, the event must be reported by submitting the completed SAE form to the contact numbers provided in the form.

The sponsor will work with the investigator to ensure that all the necessary information is provided within one calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs.

The event must be documented in source documentation and the eCRF. The following steps will be taken to report promptly and document accurately any SAE, whether or not it appears to be related to study drug(s):

1. Report the SAE to the sponsor by entering the information into the eCRF within 24 hours after becoming aware that a participant has experienced an SAE. If unable to access the eCRF, the event must be reported by submitting the completed SAE form by e-mail to clinicalsafety@horizontherapeutics.com or fax within 24 hours after becoming aware that a participant has experienced an SAE.
2. Perform appropriate diagnostic tests and therapeutic measures, and submit all follow-up substantiating data, such as diagnostic test reports, hospital discharge summaries, and autopsy report to the sponsor's representative.
3. Respond in a timely manner to any queries from sponsor regarding the SAE.
4. Conduct appropriate consultation and follow-up evaluation until the SAE is resolved, stabilized, or otherwise explained by the investigator.
5. Review each SAE report and evaluate the relationship of the SAE to study drugs.
   a. If not related to study drug but related to a study procedure or study activity, this should be noted within the SAE narrative.
6. Each investigator must report all AEs or SAEs to its IRB or IEC in accordance with IRB or IEC requirements.

After receipt of the initial report, the information will be reviewed and the investigator may be contacted with requests for additional information or for data clarification.

Follow-up will be obtained via the eCRF, fax, or e-mail, as necessary, until the event resolves or attains a stable outcome. Follow-up must be reported within 24 hours after the investigator becomes aware of it.

Sponsor or designee is responsible for notifying the relevant regulatory authorities of certain events. Notification of the IRB or IEC of all SAEs that occur at the investigator's site is the responsibility of the investigator. Investigators will be notified of all unexpected, serious, drug-related events (7- and 15- Day Safety Reports) that occur at other investigative sites during the clinical study. Each investigator is responsible for notifying its IRB or IEC of these additional SAEs.

Review of Adverse Events and Emerging New Safety Information

The sponsor will perform an ongoing review of all AEs and all other emerging new information relevant to the safety of the drug, including periodic review and analyses of cumulative safety data for the study.

The sponsor will notify all investigators involved in the clinical investigation of important safety information regarding the study treatment, as required by the applicable regulations. Investigators will notify their IRB of all such notifications, as required.

Reporting of Expedited Safety Information

The sponsor will notify the regulatory agencies and all investigators on any new serious risks associated with the drug and comply with country-specific regulatory requirements relating to safety reporting.

Development Safety Update Reports

The sponsor or designee will prepare and submit annual safety reports to competent authorities.

10.3 Appendix 3: Contraceptive and Barrier Guidance

10.3.1 Definitions

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

- Following menarche
- From the time of menarche until becoming postmenopausal unless permanently sterile (see below)
- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (> 40 IU/L or mIU/mL) is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

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

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

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenopausal female with permanent infertility due to one of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (> 40 IU/L or mIU/mL) is required.
    - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.3.2 Contraceptives Allowed During the Study

Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

Highly effective contraceptive methods have a failure rate of < 1% per year.

Note: Mycophenolate affects the metabolism and may reduce the effectiveness of hormonal contraceptives in participants who are receiving mycophenolate mofetil or mycophenolic acid and hormonal contraceptives for birth control. The participant must employ an additional contraceptive method (eg, barrier method).

CONTRACEPTIVES [a] ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods [b] That Have Low User Dependency Failure rate of < 1% per year when used consistently and correctly.
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation [c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.

CONTRACEPTIVES [a] ALLOWED DURING THE STUDY INCLUDE:

Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods [b] That Are User Dependent Failure rate of < 1% per year when used consistently and correctly.
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation [c] o oral o intravaginal o transdermal o injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation [c] o oral o injectable
• Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the investigational product (IP). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

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

10.4 Appendix 4: Liver Safety Guidelines

10.4.1 Liver Safety

Liver Chemistry Stopping Criteria and Follow-Up Assessments

ALT or AST-absolute	**ALT or AST ≥ 5 x ULN**
ALT or AST Increase	ALT or AST ≥ 3 x ULN persists for ≥ 4 weeks
Bilirubin [a, b]	ALT or AST ≥ 3 x ULN and total bilirubin ≥ 2 x ULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥ 2 x ULN, and direct bilirubin > 2 x ULN and at least doubled from baseline value)
INR [b]	ALT or AST ≥ 3 x ULN and INR > 1.5
Cannot Monitor	ALT or AST ≥ 3 x ULN and cannot be monitored weekly for 4 weeks
Symptomatic [c]	ALT or AST ≥ 3 x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions, Monitoring, and Follow-up Assessments

Actions	Follow-Up Assessments
• **Immediately** discontinue IP. • Report the event to Horizon Therapeutics **within 24 hours.** • Complete the liver event CRF and complete a SAE CRF if the event also met the criteria for an SAE. [b] • Perform follow-up assessments as described in the Follow-Up Assessment column. • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline. • **MONITORING:** • **<u>If ALT or AST ≥ 3 x ULN and total bilirubin ≥ 2 x ULN or INR > 1.5:</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up assessments within **24 hours.** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline. • A hepatology consultation is recommended. • **<u>If ALT or AST ≥ 3 x ULN and total bilirubin < 2 x ULN and INR ≤ 1.5:</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.	• Viral hepatitis serology [d] • Obtain blood sample for PK analysis within 100 days after the most recent dose [e]. • Obtain CPK, LDH, GGT, GLDH, and serum albumin. • Fractionate bilirubin, if total bilirubin ≥ 2 x ULN. • Obtain complete blood count with differential to assess eosinophilia. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event CRF. • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications CRF. • Record alcohol use on the liver event alcohol intake form. • If ALT or AST ≥ 3 x ULN **and** total bilirubin ≥ 2 x ULN or INR > 1.5 obtain the following in addition to the assessments listed above: • Antinuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG, or gamma globulins • Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week.

Liver Chemistry Stopping Criteria and Follow-Up Assessments

• **Do not restart/rechallenge** participant with IP. • Permanently discontinue IP and continue participant in the study for any protocol-specified follow-up assessments.	• Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease; complete liver imaging form • Liver [redacted] may be considered and discussed with local specialist if available, for instance: • In participants when serology raises the possibility of AIH • In participants when suspected DILI progresses or fails to resolve on withdrawal of IP • In participants with acute or chronic atypical presentation • If liver [redacted] conducted complete liver [redacted] form

AIH = autoimmune hepatitis; ALT = alanine transaminase; AST = aspartate transaminase; CPK = serum creatine phosphokinase; CRF = case report form; DILI = drug-induced liver injury; GGT = gamma-glutamyltransferase; GLDH = glutamate dehydrogenase; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; IgG = immunoglobulin G, IgM= immunoglobulin M; INR = international normalized ratio ; IP = investigational product; LDH = lactate dehydrogenase; PCR = polymerase chain reaction; PK = pharmacokinetics; SAE = serious adverse event; ULN = upper limit of normal.

a Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, record the absence/presence of detectable urinary bilirubin on dipstick which is indicative of direct bilirubin elevations suggesting liver injury.

b All events of ALT ≥ 3 x ULN and total bilirubin ≥ 2 x ULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin > 2xULN, and direct bilirubin ≥ 2xULN and at least doubled from baseline value) or ALT ≥ 3 x ULN and INR > 1.5 may indicate severe liver injury (possible 'Hy's Law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria met (excluding studies of hepatic impairment or cirrhosis). The INR stated threshold value will not apply to participants receiving anticoagulants.

c New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

d Includes: Hepatitis A IgM antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody. In those with underlying chronic hepatitis B at study entry (identified by positive HBsAg) quantitative hepatitis B DNA and hepatitis delta antibody. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) (Le Gal et al, 2005).

e PK sample may not be required for participants known to be receiving placebo or noncomparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of IP prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated or a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping will be in a separate laboratory manual provided to the sites.

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention

Criterion	Actions
ALT or AST ≥ 3 x ULN and < 5 x ULN **and** total bilirubin < 2 x ULN, or INR < 1.5, **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify Horizon Therapeutics within **24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue IP. • Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin) until the abnormalities resolve, stabilize, or return to baseline. • If at any time, the participant meets liver chemistry stopping criteria, proceed as described in the previous table ("Liver Chemistry Stopping Criteria and Follow-Up Assessments"). • If, after 4 weeks of monitoring, ALT or AST < 3 x ULN and total bilirubin < 2 x ULN, monitor participants twice monthly until liver chemistry tests resolve, stabilize, or return to baseline.

ALT = alanine transaminase; AST = aspartate transaminase; INR = international normalized ratio; IP = investigational product; ULN = upper limit of normal.

10.5 Appendix 5: National Institute of Allergy and Infectious Disease and Food and Allergy Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

National Institute of Allergy and Infectious Disease and Food and Allergy Anaphylaxis Network define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death (Sampson et al, 2006). They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (Category 1) to > 95% of all cases of anaphylaxis (for all 3 categories):

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips, tongue, uvula), and **at least** one of the following:
    a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory function [PEF], hypoxemia).
    b. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that participant (minutes to several hours):
    a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula).
    b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).
    c. Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).
    d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).
3. Reduced blood pressure after exposure to known allergen for that participant (minutes to several hours):
    a. Infants and children ─ low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure.
    b. Adults ─ systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that participant's baseline.

10.6 Appendix 6: Opportunistic Infections

Pathogens and/or Presentations of Specific Pathogens to be Considered as Opportunistic (or 'Indicator') Infections in the Setting of Biologic Therapy (Level of Evidence I-V)

Definite [a, b]	**Probable** [c]
Pneumocystis jirovecii (II)	*Paracoccidioides infections (V)*
BK virus disease including PVAN (V)	*Penicillium marneffei (V)*
Cytomegalovirus disease (V)	*Sporothrix schenckii (V)*
Post-transplant lymphoproliferative disorder (EBV) (V)	Cryptosporidium species (chronic disease only) (IV)
Progressive multifocal leukoencephalopathy (IV)	Microsporidiosis (IV)
Bartonellosis (disseminated disease only) (V)	Leishmaniasis (Visceral only) (IV)
Blastomycosis (IV)	Trypanosoma cruzi infection (Chagas' disease) (disseminated disease only) (V)
Toxoplasmosis (IV)	Campylobacteriosis (invasive disease only) (V)
Coccidioidomycosis (II)	Shigellosis (invasive disease only) (V)
Histoplasmosis (II)	Vibriosis (invasive disease due to *Vibrio vulnificus*) (V)
Aspergillosis (invasive disease only) (II)	HCV progression (V)
Candidiasis (invasive disease or pharyngeal) (II)	
Cryptococcosis (II)	
Other invasive fungi: Mucormycosis (zygomycosis) (Rhizopus, Mucor and Lichtheimia), *Scedosporium/Pseudallescheria boydii, Fusarium* (II)	
Legionellosis (II)	
Listeria monocytogenes (invasive disease only) (II)	
Tuberculosis (I)	
Nocardiosis (II)	
Non-tuberculous mycobacterium disease (II)	
Salmonellosis (invasive disease only) (II)	
HBV reactivation (IV)	
Herpes simplex (invasive disease only) (IV)	
Herpes zoster (any form) (II)	
Strongyloides (hyperinfection syndrome and disseminated forms only) (IV)	

EBV = Epstein-Barr virus; HBV = hepatitis B virus; HCV = hepatitis C virus; PVAN = polyomavirus-associated nephropathy.

a Generally does not occur in the absence of immunosuppression and whose presence suggests a severe alteration in host immunity.

b Can occur in participants without recognized forms of immunosuppression, but whose presence indicates a potential or likely alteration in host immunity.

c Published data are currently lacking, but expert opinion believes that risk is likely elevated in the setting of biologic therapy.

Source: Winthrop et al, 2015

10.7 Appendix 7: Prior Protocol Schedule of Assessments

Table 1 Schedule of Activities

Period	**Screening** [a]	**Randomized Control Period**						**Open-Label Extension**							**SFU**	
Week	**D -28 to -1**	[redacted]													**Wk 52** [c]	**Wk 56** [d]
Visit Window (Days)	**-**														**± 7**	**± 7**
Visit Number	**1**														**15**	**16**
General Procedures																
Informed consent	X															
Medical history – include Raynaud's arthritis	X															
Inclusion/exclusion criteria review	X															
Demographic data	X															
Height	X															
Eligibility review [e]		X														
Randomization		X														
Patient-Reported Outcomes [f]																
[redacted]																

Period	Screening [a]	Randomized Control Period						Open-Label Extension						SFU	
Week	D -28 to -1													Wk 52 [c]	Wk 56 [d]
Visit Window (Days)	-													± 7	± 7
Visit Number	1													15	16
Physician Assessments															
PhGDA	X	X	X	X	X	X	X	X	X	X	X	X	X		X
MMT8 bilateral	X	X	X	X	X	X	X	X	X	X	X	X	X		X
CDASI		X	X	X	X			X			X			X		
Steroid taper if stable or improving			X	X	X	X	X	X	X	X	X	X	X			
Physical examination[i]	X							X						X		
Weight	X	X						X						X		
Vital signs[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
12-lead ECG [k]	X							X						X		

Period	**Screening** [a]	**Randomized Control Period**						**Open-Label Extension**						**SFU**	
Week	**D -28 to -1**													**Wk 52** [c]	**Wk 56** [d]
Visit Window (Days)	**-**													**± 7**	**± 7**
Visit Number	**1**													**15**	**16**
Laboratory Assessments															
TB assessment [n]	X														
Anti Jo-1 antibody	X														
Serum virology [o]	X														
Estradiol and FSH [p]	X														
Pregnancy (serum βhCG) test [q]	X														
Pregnancy (urine) test [q]		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Routine chemistry [r]	X	X	X	X	X			X			X			X		X
Hematology (CBC with differential)	X	X	X	X	X			X			X			X		X
Urinalysis [s]	X	X						X						X		
Enzymes: aldolase, CK, ALT, AST, LDH	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
MSA		X						X						X		
Daxdilimab PK (serum) [t]		X	X	X	X	X		X			X			X		X

Period	Screening [a]	Randomized Control Period						Open-Label Extension						SFU	
Week	D -28 to -1	[redacted]												Wk 52 [c]	Wk 56 [d]
Visit Window (Days)	-													± 7	± 7
Visit Number	1													15	16
[redacted]															
Administration of IP															
Administration of IP [w]		X	X	X	X	X	X	X	X	X	X	X	X			
Safety															
Local injection tolerability [x]		X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant medications	Continuous														
AEs, SAEs, and/or AESIs	Continuous														

AE = adverse event; ADA = antidrug antibody; AESI = AE of special interest; ALT = alanine transaminase; AST = aspartate transaminase; βhCG = β-human chorionic gonadotropin; CBC = complete blood count; CDASI = cutaneous dermatomyositis disease area and severity index; CK = creatine kinase; DC = dendritic cells; ECG = electrocardiogram; [redacted]; FSH = follicle-stimulating hormone; [redacted] IFN = interferon; IP = investigational product; LDH = lactate dehydrogenase; [redacted]; MMT = manual muscle testing; [redacted]; MSA = myositis-specific antibodies; [redacted] PhGDA = physician global disease activity; PK = pharmacokinetics; [redacted] SAE = serious AE; [redacted] SFU = safety follow-up; [redacted]; TB = tuberculosis; Wk = week; X = to be performed.

a With approval of the medical monitor, Screening could be extended for 2 weeks in the event of delayed laboratory results.

b Week 48 will correspond to the End of Investigational Product Visit if the participant discontinues IP prior to Week 44. Participants who complete the Week 48 visit may be offered to participate in a long-term extension study for safety and efficacy. Participants who enter this study directly after completion of the Week 48 visit will not complete the visits of the SFU period.

c Week 52 visit may be performed as a phone call to the participant.
d Week 56 or earlier will correspond to the End of Study/Early Termination Visit if the participant withdraws consent to participate in the study.
e Participant eligibility (based on Screening assessments, including nonlaboratory-based assessments at Baseline [Day 1] as per the inclusion and exclusion criteria) must be checked on Day 1 prior to Randomization.
f Questionnaires should be completed before any other procedures are performed.
[redacted]
i A complete physical examination at Screening and at Weeks 24 and 48 including assessment of head, ears, eyes, nose, throat, lungs, heart, abdomen, skin, and extremities.
j Vital signs include systolic and diastolic blood pressure obtained after at least 5 minutes at rest in a seated position, heart rate, respiratory rate (breaths/min), and body temperature.
k Should be performed after 10 minutes rest in supine position and after vital signs are collected.
[redacted]
n The results of an IFNγ release assay (ie, QuantiFERON-TB Gold Plus or T-SPOT) performed within 12 weeks of the Screening visit (if available) are acceptable, provided there is no reason to suspect any re-exposure.
o Serum virology does not have to be repeated if performed within 12 weeks prior to Screening (eg, Rescreening). Table 9 shows a complete list of serology assessments.
p To confirm postmenopausal status, as appropriate. Estradiol and FSH tests do not have to be repeated if performed within 12 weeks prior to Screening (eg, Rescreening).
q In women of childbearing potential or women who are postmenopausal for less than 2 years prior to Screening, have nontherapy-induced amenorrhea for less than 12 months prior to Screening, or are not surgically sterile (absence of fallopian tubes, ovaries and/or uterus).
r Go to Table 9 for a complete list of routine laboratory assessments.
s Urine collection can be postponed for up to 14 days in women with menstrual bleeding or a urinary tract infection at the scheduled visit. Go to Table 9 for a complete list of routine urinalysis assessments.
t Serum daxdilimab PK will be obtained at Day 1 at approximately 2 hours or longer postdose, predose on Day 1 and Weeks 4, 8, 12, 16, 24, and 36; and any time on Weeks 48 and 56.
[redacted]
v Collection at Day 1 (required) and at-home collection (fingerstick) at 1 week (optional).
w The visit window for the IP administration is ± 3 days. If a visit and dosing is outside the visit window, a protocol deviation will be noted, and IP may be administered within the -13 days +14 days as a remedial dosing window. Except for local injection tolerability (footnote x), on days of administration of IP, all procedures and blood sampling must be collected before the administration.
x To be performed 30 minutes post-dose (can be performed any time at Week 48 as no IP is administered).

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