A PHASE 2A, OPEN LABEL, PROOF-OF-CONCEPT TRIAL OF DAXDILIMAB FOR THE TREATMENT OF MODERATE-TO-SEVERE ALOPECIA AREATA

PROTOCOL HZNP-DAX-201

Investigational New Drug (IND) Number: 158932

FINAL

VERSION 2.0

07 JAN 2022

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[redacted]

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PROTOCOL VERSION HISTORY

Version	Rationale for amendment	Main changes to the protocol
1.0 / 19 NOV 2021	Initial version	N/A
2.0 / 07 JAN 2022	To update the address of Horizon Therapeutics Ireland DAC.	Cover page: The address was updated for Horizon Therapeutics Ireland DAC to the new address.
	To add a restriction on egg retrieval/egg donation for female participants of childbearing potential to Inclusion Criterion #9.	Section 1.1 (Synopsis) and Section 5.1 (Inclusion Criteria): Restriction on egg retrieval/egg donation was added to Inclusion Criterion #9: 'the participant must agree to use a highly effective contraceptive method from at least 4 weeks prior to Day 1 until at least 6 months (approximately 5 half-lives) after the last IP administration or the end of the trial, whichever is longer, *and refrain from egg retrieval/egg donation during this period*.'
	To reduce the duration of participant's sample storage by the Sponsor from 25 years to 15 years.	Section 10.9 (Biological Specimens and Data): The duration for storage of participant's sample(s) by the Sponsor after the end of the study was reduced from 25 years to 15 years.
	To update the citation hyperlink in Appendix 3 to the correct reference.	[redacted]

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and applicable local regulations. The principal investigator will assure that no planned deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the institutional review board (IRB)/research ethics board (REB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed ICH GCP training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB/REB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB/REB before the changes are implemented to the study. All changes to the consent form will be IRB/REB approved.

SIGNATURE PAGE

The signatures below constitute the approval of this protocol and provide the necessary assurances that this trial will be conducted according to this protocol, applicable local regulations, and ICH GCP guidelines.

Name	Title	Signature and date (DD-MMM-YYYY)
[redacted], MD	Executive Medical Director Horizon Therapeutics	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 07-Jan-2022 | 12:38:27 CST BE79887EED2B48A8AE7BF3AC7D639383 07-Jan-2022 | 12:38:38 CST
[redacted], PhD	Sr. Director, Biostatistics, Biometrics Horizon Therapeutics	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 07-Jan-2022 | 13:07:27 CST 94348E43E05145848D3DCFDE0A20F5C3 07-Jan-2022 | 13:07:31 CST
[redacted], BSc	Director, Scientific and Regulatory Affairs Innovaderm Research Inc.	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 07-Jan-2022 | 14:13:25 EST 7B587BB5D1784033A925A4345557A0A4 07-Jan-2022 | 14:13:27 EST

PRINCIPAL/QUALIFIED INVESTIGATOR SIGNATURE PAGE

Investigator Name: _____

Signature: _____ **Date:** _____
(DD-MMM-YYYY)

Institution Name: _____

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with the protocol, informed consent, institutional review board/independent ethics committee procedures, instructions from sponsor's representatives, ICH GCP guidelines, and applicable local regulations governing the conduct of clinical studies.

LIST OF ABBREVIATIONS

Abbreviation	Definition
AA	alopecia areata
ADA	anti-drug antibodies
ADCC	antibody-dependent cellular cytotoxicity
ADR	adverse drug reactions
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
[redacted]	[redacted]
ALT	alanine aminotransferase
anti-HBc	antibody to hepatitis B core antigen
AST	aspartate aminotransferase
BDCA2	blood dendritic cell antigen 2
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CK	creatine kinase
Cl	clearance
CLASI-A	Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity
CLE	cutaneous lupus erythematosus
[redacted]	[redacted]
CONSORT	Consolidated Standards of Reporting Trials
C_{max}	maximum observed concentration
CMV	cytomegalovirus
COVID-19	Coronavirus Disease 2019
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology for Adverse Events
DC	dendritic cell
DCNB	dinitrochlorobenzene
DM	dermatomyositis
DMARD	disease-modifying antirheumatic drug
DPCP	diphenylcycloprophenone
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transferase

Abbreviation	Definition
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin
HEENT	head, eyes, ears, nose, throat
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IFN	interferon
Ig	immunoglobulin
IgG1λ	immunoglobulin G1 lambda
ILT7	immunoglobulin-like transcript 7
IND	Investigational New Drug
IP	investigational product
ITT	intention-to-treat
IRB	institutional review board
IV	intravenous
IVIg	intravenous immunoglobulin
JAK	Janus Kinase
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MPV	mean platelet volume
[redacted]	[redacted]
N/A	not applicable
NK	natural killer
NKG2D	natural killer receptor D
PBMCs	peripheral blood mononuclear cells
PD	pharmacodynamic
pDC	plasmacytoid dendritic cell
PK	pharmacokinetic
PLT	platelet
PM	polymyositis
PPD	purified protein derivative
PT	Preferred Term
PUVA	psoralen-UV-A
Q4W	every 4 weeks

Abbreviation	Definition
QC	quality control
RBC	red blood cell (count)
REB	research ethics board
SAE	serious adverse event
SALT	Severity of Alopecia Tool
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneously
SD	standard deviation
SID	sample identification
SLE	systemic lupus erythematosus
SOC	System Organ Class
$t_{1/2}$	half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse events
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
UV	ultraviolet
V_{ss}	volume of distribution at steady state
WBC	white blood cell (count)
WHO-DD	world health organization drug dictionary
WK	week
WOCBP	women of childbearing potential

1 PROTOCOL SUMMARY

1.1 Synopsis

Name of Sponsor/Company:	**Name of Investigational Product:**	**Name of Active Ingredient:**
Horizon Therapeutics Ireland DAC	Daxdilimab (HZN-7734)	Daxdilimab (HZN-7734)

Protocol Title:

A Phase 2a, Open Label, Proof-of-Concept Trial of Daxdilimab for the Treatment of Moderate-to-Severe Alopecia Areata

Phase of Development:

Phase 2a

Trial Center(s):

This trial will be conducted at approximately 8 sites located in Canada and the United States.

Number of Participants (planned):

The trial is planned to enroll approximately 30 participants with alopecia areata (AA).

Duration of Trial:

The maximum trial duration per participant is approximately 52 weeks, including up to 30 days for the screening period, 32 weeks for the open-label treatment period where participants will receive daxdilimab [redacted] mg [redacted], and approximately [redacted] for the follow-up period.

Investigational Product, Dosage, and Mode of Administration:

Daxdilimab will be provided as a [redacted].

All participants will receive daxdilimab [redacted] mg administered subcutaneously as two 1.5 mL injections [redacted]. All investigational product (IP) administration will be done at the clinical site by the trial staff. On [redacted] and [redacted] participants will remain under observation for at least 1 hour after IP administration.

Reference therapy, dosage and mode of administration:

Not applicable (N/A).

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Objectives and Endpoints:

Primary Objective and Endpoint

Efficacy Objective	**Efficacy Endpoint**
To evaluate the effect of daxdilimab on reducing hair loss at Week 24 in participants with AA.	Percent change from baseline in Severity of Alopecia Tool (SALT) score at Week 24.

Secondary Objectives and Endpoints

Efficacy Objectives	**Efficacy Endpoints**
To evaluate the effect of daxdilimab on reducing hair loss through 9 months of treatment in participants with AA.	• Percent change from baseline in SALT score at Weeks 12-20; 28-36. • Proportion of participants who achieve ≥50% reduction in SALT from baseline at Weeks 12-36. • Proportion of participants with absolute SALT score ≤ 10, 20, 30, 50 at Weeks 12-36.
To evaluate the post-treatment duration effect of daxdilimab on reducing hair loss in participants with AA.	• Percent change from baseline in SALT score at Weeks 40-48. • Proportion of participants who achieve ≥50% reduction in SALT from baseline at Weeks 40-48. • Proportion of participants with absolute SALT score ≤ 10, 20, 30, 50 at Weeks 40-48.
Pharmacokinetic (PK)/ Pharmacodynamic (PD)/ Immunogenicity Objectives	**PK/PD/Immunogenicity Endpoints**
To characterize the PK, PD, and immunogenicity of daxdilimab.	• Daxdilimab concentrations. • Change from baseline in plasmacytoid dendritic cells (pDCs). • Anti-drug antibody (ADA) rate.
Safety Objective	**Safety Endpoints**
To evaluate the safety and tolerability of daxdilimab.	• Incidence of adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs).

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Exploratory Objectives and Endpoints

Efficacy Objective	**Efficacy Endpoints**
[redacted]	• [redacted] • [redacted] • [redacted] • [redacted] • [redacted]
[redacted]	[redacted]
[redacted]	• [redacted]

Trial Design:

This is a Phase 2a, multicenter, open-label, proof-of-concept trial to assess the preliminary efficacy, safety, tolerability, PK, and PD of daxdilimab in participants with moderate-to-severe AA, with ≥50% and ≤95% total scalp hair loss as defined by the SALT score at Screening and Day 1. Participants will be between 18 and 65 years of age (inclusive), with a current episode of hair loss of >3 months but <7 years, along with investigator's assessment that hair regrowth is possible and no evidence of active regrowth present at baseline, and no known history of significant regrowth during the last 6 months. Approximately 30 participants will be enrolled to receive daxdilimab [redacted] mg administered subcutaneously [redacted].

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

The trial will comprise of a screening period of up to 30 days with enrollment on Day 1. Participants will be treated with daxdilimab [redacted] mg [redacted]. The primary endpoint assessment will

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occur during the Week 24 visit. All participants will have a follow-up period of 16 weeks (through Week 48) to evaluate long-term safety and to observe the duration of efficacy following the treatment period. Participants who prematurely stop dosing will be followed through Week 48 unless participants withdraw consent of trial participation or are lost to follow-up. Any participant who discontinues from the trial prematurely and does not plan to participate in the post-treatment follow-up period will be requested to complete the early termination (ET) visit.

For scheduled trial visits, participants will come to the trial centers on 14 occasions: screening, [redacted].

Efficacy will be evaluated by assessment of SALT scores, [redacted].

Blood samples will be collected from all participants to characterize the PK, PD, and immunogenicity of daxdilimab.

Safety will be assessed by collecting AEs, SAEs, AESIs, performing local injection site tolerability assessment, recording vital signs, performing physical examinations and ECGs, and evaluating clinical laboratory results.

Inclusion/Exclusion Criteria:

Inclusion Criteria

All participants must meet all of the following criteria to be eligible for trial participation, either at the screening and Day 1 visits, or only at one of the specified visits (screening or Day 1) as noted in the criterion:

1. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the United States,) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations.
2. Adult men and women, aged 18 to 65 years, inclusive, at the time of informed consent.
3. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial.
4. Willing to keep the same hair style and color (eg, hair products, process, and timing for hair appointments) for the duration of the trial.
5. Clinical diagnosis of moderate-to-severe AA - defined as the presence of $\geq$ 50% and $\leq$ 95% total scalp hair loss at screening and baseline (Day 1) defined by the SALT score.
6. Duration of current episode of hair loss >3 months but <7 years at screening and Day 1, along with investigators' assessment that hair regrowth is possible. Total duration since diagnosis of AA could be >7 years.

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7. No evidence of active regrowth present at baseline and no known history of significant regrowth, as per investigator's judgement, over the last 6 months.
8. Female of childbearing potential must have a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1.
9. For female participant of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the participant must agree to use a highly effective contraceptive method from at least 4 weeks prior to Day 1 until at least 6 months (approximately 5 half-lives) after the last IP administration or the end of the trial, whichever is longer, and refrain from egg retrieval/egg donation during this period. Highly effective contraceptive methods include hormonal contraceptives (e.g, combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s) (provided his vasectomy was performed ≥4 months prior to Screening), tubal ligation or double barrier methods of contraception (e.g. male condom with cervical cap, male condom with diaphragm, and male condom with contraceptive sponge) in conjunction with spermicide.

   Note: For countries where double barrier methods are not accepted as highly effective contraception, this option must not be considered.

   Note: Participants must have been on a stable dose of hormonal contraceptives for at least 4 weeks before Day 1.

   Note: The above list of contraceptive methods does not apply to participants who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal intercourse throughout the trial and for at least 6 months after the last IP administration or until the end of the trial, whichever is longer. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not acceptable.

   Note: A female participant of nonchildbearing potential is defined as follows:
   - Female participant who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy).
   - Female participant who has had a cessation of menses for at least 12 months prior to the screening visit without an alternative medical cause, and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels).
10. For male participant involved in any sexual intercourse that could lead to pregnancy, participant must agree to use one of the highly effective contraceptive methods listed in Inclusion Criterion #9, from Day 1 until at least 6 months (approximately 5 half-lives) after the last IP administration and refrain from donating sperm during this period. If the female partner of a male participant uses any of the hormonal contraceptive methods listed above, this contraceptive method should be used by the female partner from at least 4 weeks before Day 1 until at least 6 months after the last administration of daxdilimab.

Exclusion Criteria:

Participants will be ineligible for trial participation if they meet any of the following criteria at the Screening and/or Day 1 visits, as applicable:

General Exclusion Criteria

1. Individuals involved in the conduct of the trial, their employees, or immediate family members of such individuals.
2. Any clinically significant medical condition or physical/laboratory/ECG/vital signs abnormality that would, in the opinion of the investigator, put the participant at undue risk or interfere with the evaluation of the IP or interpretation of trial results.
3. History of allergy, hypersensitivity reaction, or anaphylaxis to any component of the IP or to a previous monoclonal antibody (mAb) or human immunoglobulin (Ig) therapy.
4. Participant has had excessive sun exposure, is planning a trip to a sunny climate, or has used tanning booths within 4 weeks prior to Day 1 or is not willing to minimize natural and artificial sunlight exposure during the trial. Use of sunscreen products and protective apparel are recommended when sun exposure cannot be avoided.
5. Spontaneous or induced abortion or still or live birth $\leq$ 4 weeks prior to Screening.
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 or until the end of the trial, whichever is longer.
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 trial assessments.
8. Major surgery within 8 weeks prior to Screening or elective surgery planned during the trial.
9. Known history of a primary immunodeficiency or an underlying condition such as known human immunodeficiency virus (HIV) infection, a positive result for HIV infection, splenectomy, or any underlying condition that in the opinion of the investigator significantly predisposes the participant to infection.
10. At Screening, any of the following (tests may be repeated once within the same Screening period to confirm results prior to Day 1):
    - Aspartate aminotransferase (AST) > 2.5× upper limit of normal (ULN)
    - Alanine aminotransferase (ALT) > 2.5× ULN
    - Total bilirubin > 1.5× ULN (unless due to Gilbert's syndrome)
    - Serum immunoglobulin G (IgG) < 600 mg/dL (or < 6 g/L)
    - Neutrophil count < 1000/µL (or < 1.0×10^9/L)
    - Platelet count < 50,000/µL (or < 50×10^9/L)
    - Hemoglobin < 8 g/dL (or < 80 g/L)
    - Total lymphocyte count < 200 cells/mm^3
    - Glomerular filtration rate (Modification of Diet in Renal Disease [MDRD]) < 30 mL/min/1.73 m^2
    - Spot urine protein to creatinine ratio (UPCr) > 3 mg/mg

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11. Confirmed positive test for hepatitis B serology defined as:
    - Hepatitis B surface antigen (HBsAg), or
    - Hepatitis B core antibody (HBcAb or anti-HBc)
12. Positive test for hepatitis C virus antibody.
13. Active tuberculosis (TB), or a positive TB test at Screening. Participant will be evaluated for latent TB infection with a purified protein derivative (PPD) test or a QuantiFERON-TB Gold test. Participants who demonstrate evidence of latent TB infection (either PPD ≥5 mm of induration or positive QuantiFERON-TB Gold test, irrespective of bacille Calmette-Guérin vaccination status will not be allowed to participate in the trial, unless documented history of appropriate treatment for active or latent TB. Participants with an indeterminate test result can repeat the test, but if the repeat test is also indeterminate, they are excluded.
14. Any severe herpes virus family infection (including Epstein-Barr virus, cytomegalovirus [CMV]) at any time prior to Day 1, 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.
15. Any herpes zoster, CMV, or Epstein-Barr virus infection that was not completely resolved 12 weeks prior to Day 1.
16. Any of the following within 30 days prior to signing the ICF and though Day 1:
    - Clinically significant active infection in the opinion of the investigator, including ongoing, and chronic infection requiring antibiotics or antiviral medication (chronic nail infections are allowed). Note: Participant with a limited recurrence of a cold sore or herpes genitalis between ICF signature and Day 1 could be eligible based on the investigator's judgement.
    - Any infection requiring hospitalization or treatment with intravenous (IV) anti-infectives.
    - A participant with a documented positive severe acute respiratory syndrome coronavirus 2 (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 resolution of symptomatic Coronavirus Disease 2019 (COVID-19) illness.
17. Opportunistic infection requiring hospitalization or parenteral antimicrobial treatment within 2 years prior to Day 1.
18. Any acute illness or evidence of clinically significant active infection, such as fever ≥ 38.0°C (≥ 100.5°F) on Day 1.
19. History of clinically significant cardiac disease including unstable angina; myocardial infarction within 6 months prior to Day 1; congestive heart failure; arrhythmia requiring active therapy, except for clinically insignificant extra systoles, or minor conduction abnormalities; or presence of clinically significant abnormality on ECG if, in the opinion of the investigator, it would increase the risk of trial participation.

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20. History of cancer or lymphoproliferative disease within 5 years prior to Day 1, except as follows:
    - In situ carcinoma of the cervix treated with apparent success with curative therapy > 12 months prior to Screening, or
    - Nonmetastatic cutaneous basal cell or squamous cell carcinoma of the skin treated with apparent success with curative therapy.
21. Receipt of a live or live-attenuated vaccine within 8 weeks prior to Day 1 or plans to receive a live or live attenuated vaccine during the trial and up to 4 weeks after the last IP administration.
22. Nonlive and nonlive-attenuated vaccines for COVID-19 (eg, RNA-based vaccines, protein-based vaccines, and nonreplicating viral vector-based vaccines) are not allowed within 4 weeks prior to Day 1 and within 2 weeks prior to each trial visit.
23. Participant should be assessed for epidemiologic risk of COVID-19 (ie, recent exposure, high-risk housing) and for health-related risk of COVID-19 severity based on current understanding of risk factors for severe disease when making a decision regarding the individual's risk of participation. 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 enrolled.
24. 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 trial or at a blood bank donation), or plans to give blood or plasma during their participation in the trial or up to 6 months after the last IP administration, whichever is longer.
25. Transfusion with blood, packed red blood cells, platelets or treatment with plasmapheresis, or plasma exchange within 8 weeks prior to Day 1 and for the total duration of the trial participation.

<u>Disease-related Criteria</u>

26. Active forms of other inflammatory skin disease(s) or evidence of other skin conditions (eg, psoriasis, seborrheic dermatitis, lupus) at the time of the Screening and through Day 1, that in the opinion of the investigator might interfere with evaluation of AA and the assessment of the activity measures.
27. Presence of another form of alopecia (except for androgenic alopecia).
28. History of male or female pattern hair loss > Hamilton stage III or > Ludwig stage II.
29. History or presence of hair transplants.
30. History or presence of micropigmentation of the scalp (Note: microblading of the eyebrows is permitted).

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Prior and concomitant Therapy Criteria

31. Use of steroids (systemic and intralesional), anthralin, squaric acid, diphenylcycloprophenone (DPCP), dinitrochlorobenzene (DCNB), protopic, minoxidil, or any other medication which in the opinion of the investigator may affect hair regrowth within 4 weeks of Day 1 visit.

    Note: Intranasal and inhaled corticosteroids are allowed, eye and ear drops containing corticosteroids are also allowed.

32. Use of platelet-rich plasma injections in the last 12 weeks prior to Day 1.

33. Topical medicated treatment that could affect AA including, but not limited to, topical corticosteroids, calcineurin inhibitors, antimicrobials, medical devices within 2 weeks of Day 1 visit.

    Note: Topical corticosteroids are permitted outside of the scalp, eyebrows, and eyelids.

34. Participants who have had previous treatment with any biologic B-cell-depleting therapy (eg, rituximab, ocrelizumab, or ofatumumab) or other B-cell targeting therapy (eg, belimumab) within 12 months before Day 1.

35. Participants who have received previous treatment with pDC inhibiting therapies (eg, anti-ILT7, anti-blood dendritic cell antigen 2 [BDCA2]).

36. Inadequate response to adequate trial of oral Janus Kinase (JAK) inhibitors. Previous exposure to topical JAK inhibitors is acceptable, regardless of response.

37. Any biologic or conventional disease-modifying antirheumatic drugs (DMARD), immunosuppressant (eg, cyclosporine, methotrexate, or azathioprine), JAK-inhibitors, interferon (IFN) blocking therapies, or antiproliferative agents, if last dose was taken:

    a. within 8 weeks prior to Day 1 or

    b. drug-specific 5 half-lives elimination period (if longer than 8 weeks).

38. Participant has received any marketed or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.

39. Currently receiving a nonbiological IP or device or has received one within 4 weeks prior to Day 1 or within 5 published half-lives, whichever is longer.

40. Participant has received any ultraviolet (UV)-B phototherapy (including tanning beds), has had psoralen-UV-A (PUVA) treatment, or excimer laser within 4 weeks prior to Day 1.

Statistical methods:

Continuous variables will be summarized in tables and will include the number of participants, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be presented in

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tables as frequencies and percentages. A statistical analysis plan (SAP) will provide additional details on the approach to the analysis and data displays.

Efficacy Analyses

The percent change from baseline in SALT score at Week 24 will be summarized with descriptive statistics. All other efficacy endpoints will be analyzed descriptively, with summary statistics for continuous endpoints and frequency distribution for binary endpoints.

Safety Analyses

The occurrence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and adverse events of special interest AESIs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT), as well as by severity and by relationship to the IP.

Other safety parameters, including but not limiting to laboratory assessments and vital signs will also be summarized as appropriate.

Pharmacodynamic and Biomarker Analyses

The observed count along with the change and percent change from baseline will be summarized descriptively as appropriate.

Pharmacokinetic Analysis

Serum concentrations will be summarized descriptively by visit. Additional PK analyses may be conducted as appropriate and reported separately from the clinical study report.

Anti-drug-antibodies

Anti-drug-antibody (ADA) rate will be summarized descriptively.

Planned Analyses

The primary analysis will be performed when the last participant has completed Week 24 or withdraws prior to the scheduled Week 24 visit. All available data at the time of the data cut-off (including data collected after Week 24) will be included in the primary analysis.

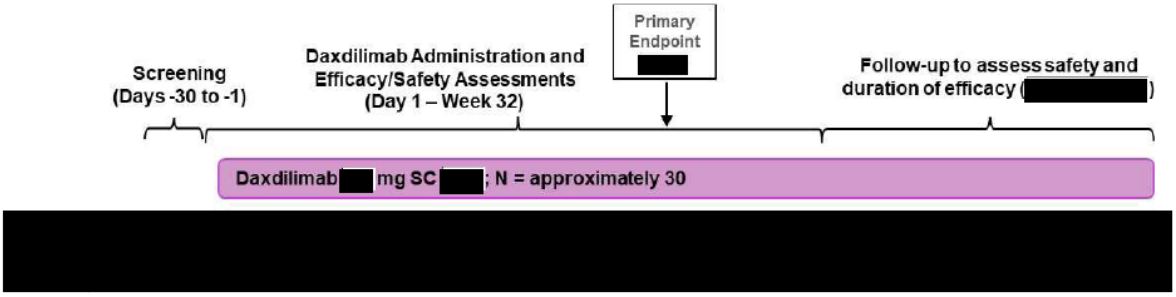
The final analysis will be performed when all participants have completed trial.

Sample Size Consideration:

A total of up to 30 participants will receive daxdilimab in the trial. The sample size was determined by the need to evaluate potential efficacy, safety and tolerability, and PK/PD. No formal power calculation was performed.

1.2 Trial Diagram

Figure 1: Trial Diagram



Abbreviations: SC, subcutaneously; [redacted] WK, week.

1.3 Schedule of Assessments

The screening evaluation will only be performed after the participant has agreed to participate and has signed and dated the ICF. No treatment or trial-related procedures will be initiated before the informed consent is signed. The Day 1 visit must be performed, at the latest, 30 days after the screening visit.

The screening evaluation will be performed according to the inclusion and exclusion criteria. If the participant fulfills all inclusion criteria and no exclusion criteria, he or she may be enrolled in the trial.

Table 1 provides a description of the procedures to be performed at each visit.

Unless specified otherwise, the trial assessments scheduled on Day 1 must be performed before the IP administration. The recommended order for performing the trial assessments is as follows (applicable to all visits), except for collection of blood samples for analysis of serum daxdilimab ADA and PK samples, which must be performed prior to IP administration at the visits specified in Table 1 (refer to footnotes):

- Investigator assessments
- Vital signs
- 12-lead ECG
- Medical photographs
- Blood draw

Table 1: Schedule of Assessments

Procedure															
Window (days)															
Informed consent	X														
Demographics	X														
Medical and surgical history	X	X													
Inclusion/exclusion criteria	X	X													
Height	X														
Body weight	X				X			X			X			X	X
Physical examination[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests (biochemistry, hematology, and urinalysis)[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serology testing (HIV, HCV and HBV [HBsAg, HBcAb or anti-HBc])	X														
12-lead ECG[5]	X	X						X						X	X
Pregnancy testing[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TB evaluation[7]	X														
SALT assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical photography[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Whole blood transcriptomics		X	X		X			X		X	X			X	X
DC flow cytometry	X	X	X		X			X		X	X			X	X
PBMCs		X	X					X		X					

Procedure **Window (days)**	[redacted]													
Serum biomarkers	X	X	X		X			X		X	X			X	X
Plasma biomarkers	X	X	X		X			X		X	X			X	X
Blood MxA		X	X		X			X		X	X			X	X
[redacted]															
Daxdilimab serum PK testing[10]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum daxdilimab ADA[11]		X	X	X	X			X			X			X	X
[redacted]															
Concomitant medication monitoring	Continuous														
Adverse event monitoring (AEs, SAEs, and/or AESIs)	Continuous														

Abbreviations: ADA, anti-drug antibodies; AE, adverse event; AESI, adverse event of special interest; anti-HBc, antibody to hepatitis B core antigen; ALODEX, Alopecia Density and Extent; HBsAg, Hepatitis B surface antigen; ClinRO, Clinician Reported Outcome; DC, dendritic cell; ECG, electrocardiogram; EOT, end of treatment; ET, early termination; HBcAb, hepatitis B core antibody; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; IP, investigational product; MxA, myoxvirus protein A; PBMCs, peripheral blood mononuclear cells; PK, pharmacokinetic; PPD, purified protein derivative; Q4W, every 4 weeks; SAE, serious adverse event; SALT, Severity of Alopecia Tool; SC, subcutaneous; TB, tuberculosis; Wk, week; WOCBP, women of childbearing potential.

[1] Participants who prematurely stop dosing will enter the post-treatment follow-up period of 16 weeks after the last dose received. Participants who do not enter the post-treatment follow-up period will be requested to complete the ET visit.

[2] A focused physical examination should be performed as described in Section 8.5.2.

[3] Vital signs comprise heart rate, blood pressure, temperature, and respiratory rate. Vital signs will be performed pre-dose during the Treatment Period.

[4] Laboratory tests will be performed pre-dose during the Treatment Period.

[5] 12-lead ECG to be done pre-dose during the Treatment Period.

[6] WOCBP (see Section 5.1 for definition) will have a serum pregnancy test at screening and urine pregnancy tests at other visits.

[7] The results of an IFN-gamma release assay (ie, QuantiFERON-TB Gold performed within 12 weeks of the Screening visit (if available) are acceptable, provided there is no reason to suspect any re-exposure. If PPD is used, a second visit will be necessary for PPD reading only.

[8] Medical photographs of the full scalp will be taken for all participants, and of the eyebrows and eyelashes for participants who have hair loss in these areas at baseline.

[9] Participants will receive daxdilimab [redacted] mg administered SC on Day 1 followed by [redacted]. All IP administrations will be done at the clinical site by the trial staff. On [redacted] and [redacted], participants will remain under observation for at least 1 hour after IP administration.

[redacted]

[10] Serum daxdilimab PK will be obtained on **Day 1** at the following timepoint: 2 hours (±5 minutes) post-dose. Samples for PK will be obtained pre-dose on [redacted] and any time during the trial visit on Weeks 36-48.
[11] Collection of blood samples for analysis of serum daxdilimab ADA must be performed prior to IP administration at all applicable visits.
[12] Local injection tolerability assessments including injection site reactions will be performed approximately 30 minutes post-injection (can be performed any time at [redacted] as no IP is administered). Additional follow-up after Week 36 can be performed for any ongoing injection site reactions.

2 INTRODUCTION

2.1 Background

2.1.1 Alopecia Areata

Alopecia areata (AA) is a common acute onset autoimmune disorder characterized by transient, non-scarring hair loss in well defined areas.[1] It is the second most common form of Alopecia after the androgenetic type. The extent of hair loss defines the three main AA forms, namely Patchy AA, Alopecia Totalis (loss of all scalp hair) and Alopecia Universalis (loss of all body hair). Patchy AA is the most common form.

The risk of developing AA is estimated to be around 25% in adult-onset patients. Spontaneous regrowth can occur in 50-80% of the patchy AA cases within a year, however additional patches can also form, resulting in the formation of several patches that often coalesce eventually lead to alopecia totalis.[2] Alopecia areata overall rate of relapse has been estimated to be around 86%.[3,4] Patchy AA can also progress to alopecia universalis at any time.

Clinically, the patch of AA is usually completely bald, smooth and round or oval in shape. In the periphery of the lesions, short, less than 4 mm exclamation mark hairs and black dots are commonly observed, especially in acute stages of AA. The scalp, the beard area and the eyebrow are most commonly involved, however any hair-bearing area can be affected. One of the most important features of AA is that the disease process does not destroy hair follicles.

Alopecia areata is considered as a complex genetic disease influenced by environmental factors. Based on large epidemiologic studies from North America, Europe and Asia, and systematic meta-analysis, the lifetime incidence of AA is estimated to be around 2% of the population.[5,6] The onset is most common in the third and fourth decades of life but it does occur at any age.[7] When first onset is at an earlier age the risk for future extensive disease increases.[8]

No gender predilection has been identified, and while it was widely thought that there were no racial differences, a recent cross-sectional study of self-registered AA patients, showed higher odds of AA in African Americans and lower odds in Asians compared with whites.[5,9]

A number of comorbidities have been associated with AA, including depression, anxiety, and autoimmune diseases such as lupus erythematosus, vitiligo, psoriasis, rheumatoid arthritis, as well as asthma, thyroid disease, depression and anxiety .[8,10,11]

2.1.2 Daxdilimab

Daxdilimab (HZN7734 [previously known as MEDI7734 and VIB7734]) is a human immunoglobulin (Ig) G1 lambda (IgG1λ) afucosylated monoclonal antibody (mAb) specific for immunoglobulin-like transcript 7 (ILT7), a cell-surface protein that is unique to plasmacytoid dendritic cells (pDCs) in human and the nonhuman primate. Daxdilimab binds to ILT7 on the surface of pDCs, which leads to recruitment of macrophages and natural killer (NK) cells, thus inducing apoptosis and depletion of pDCs in vivo. The afucosylation of daxdilimab is designed to

enhance the potency of daxdilimab for antibody-dependent cellular cytotoxicity (ADCC) against pDCs. Since pDCs are the major cell type that secretes type I interferons (IFNs) in response to nucleic acid-containing immune complexes, it is hypothesized that depletion of pDCs will reduce disease activity for patients with autoimmune diseases that are partially driven by abnormally high levels of type I IFNs.

2.1.3 Trial Rationale

The exclamation hair and the bald areas are caused by the inhibition of the hair follicle cycling which represents one of the end results of the AA pathophysiologic process, which starts with the loss of immune privilege of the hair follicle and a subsequent autoimmune attack of the bulbar region of anagen phase hair follicles by CD8+ T cells and Th1 cytokines.[1,6,12]

Genome-wide association studies have identified human leukocyte antigen (HLA) region genes and other immune function genes to be associated with AA. Interestingly some of these genes had not been previously implicated in other autoimmune diseases.[6,13-15] These genes were the ULBP3/ULBP6 known to be ligands for the natural killer receptor D (NKG2D).

The significance of this finding was later demonstrated in functional studies where CD8+NKG2D+T cells were shown to be major effectors of AA pathogenesis.[16] Effector CD8 T cells can get activated by expression of MHC I and NKG2DL on epithelial cells and can exert their cytotoxic effects through IFNg. CD8 T cells are not the only immune cells involved in AA. CD4 T cells and NK cells are also present around the epithelial cells and secrete numerous pro-inflammatory cytokines, including IFNg.

Critical to the recruitment and activation of the peri- and intra-lesional NK and T cells seems to be pDCs and Type I IFNs.[17]

Early evidence of the role of IFNa in AA came from data of treatment of Hepatitis B with IFNα2a. In one study, alopecia developed in 19% of the treated patients, and it regressed soon after treatment completion.[18] These observations led to studies that searched for direct histologic evidence of Type I interferons.

Lesional scalp biopsies from patients with AA were assessed with immunohistochemistry for expression of the type 1 interferon-inducible myxovirus protein A (MxA), one of the most reliable surrogate markers of Type 1 interferons, and CXCR3, a chemokine receptor found on cytotoxic cells. Interestingly, MxA was expressed in the intradermal and subcutaneous compartments of the hair follicle including sebaceous glands in AA, but not in the epidermal compartment of AA. CXCR3 staining showed the same exact expression pattern, suggesting that Type 1 IFN attract the cytotoxic cells in the deeper areas of the skin, where the hair follicles are located.[12]

Another study using immunohistochemistry on AA biopsies, not only confirmed the expression of MxA in peribulbar areas, but also demonstrated the presence of pDCs through BDCA2 staining in the same areas. pDCs accounted for approximately 10% of the mononuclear cells, and the abundance of MxA expression suggested that the pDCs were in an active state producing Type I IFNs.[19]

Using a dynamic model of AA development, the central role of pDCs in initiating AA was demonstrated.[20] Induction of AA in mice, by intradermal injection of T cells derived from lymph nodes of AA-bearing syngeneic mice, revealed that densely infiltrated IFN-a-producing pDCs initiate the lesions in the affected hair follicle as well as in the proximity of these follicles. Additionally, intradermal injection of pDCs also induced AA.

2.2 Risk/Benefit Assessment

2.2.1 Known Potential Risks

Daxdilimab was tested in a first-in-human, single-ascending dose study (Study D6080C00001). The key objectives of the study were to evaluate the single dose safety, pharmacokinetics (PK), and pharmacodynamics (PD). The study enrolled 36 adult subjects with dermatomyositis (DM), polymyositis (PM), Sjogren's syndrome, systemic lupus erythematosus (SLE), or systemic sclerosis. Subjects received a single subcutaneous (SC) injection of daxdilimab [redacted], or [redacted] mg, or placebo. After single SC administration, serum peak concentrations were observed 5 to 8 days post-dose. Daxdilimab PK exposures increased in an approximately dose-proportional manner. Apparent clearance (CL/F) ranged from 0.468 to 1.03 L/day. Apparent volume of distribution (Vz/F) ranged from 9.89 to 19.0 L. The estimated terminal elimination half-life ($t_{1/2}$) ranged from 13 to 20 days across dose levels. No serious adverse events (SAEs) occurred that were considered related to the investigational product. Two subjects had treatment-emergent adverse events (TEAEs) considered related to the investigational product by the investigator: one subject in the placebo group with nausea (Grade 1) and one subject in the daxdilimab [redacted] mg group with tongue discolouration (Grade 1). The most common adverse events (AEs) reported in the daxdilimab-treated subjects were diarrhoea (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 anti-drug antibodies (ADAs) occurred. Mean reductions of at least 50% in the pDC level of daxdilimab-treated subjects were evident at 24 hours after dosing in all dose groups. Increasing doses were associated with a non-linear increase in pDC reduction. Increasing doses were generally associated with a longer duration of pDC reduction.

Study HZN7734.P1b.S1 evaluated the PK, PD, and safety of 3 monthly doses of daxdilimab. The study enrolled 31 subjects with SLE, cutaneous lupus erythematosus (CLE), Sjogren's syndrome, systemic sclerosis, PM, or DM. Subjects received placebo or daxdilimab at [redacted] mg by SC injection. Daxdilimab PK exposure was approximately dose proportional over the dose range investigated. Apparent steady-state clearance (CLss/F) values were similar across dose groups and ranged from 0.62 to 1.18 L/day. The $t_{1/2}$ was 14.6 days for subjects receiving [redacted] mg daxdilimab. Sixteen of 22 (72.7%) daxdilimab-treated subjects and 6 of 9 (66.7%) placebo treated subjects experienced at least one TEAE. There were no deaths in the trial. One placebo-treated subject and no daxdilimab-treated subjects experienced treatment emergent SAEs. No subject experienced an AE leading to treatment discontinuation. No treatment-emergent ADA was observed in subjects treated with daxdilimab. In subjects with CLE, Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity (CLASI-A) scores improved more in the daxdilimab [redacted] mg group than the placebo group. After 3 monthly SC doses of daxdilimab [redacted] mg or [redacted] mg, the median change in percent pDCs at Day 85 was -54.1% in the daxdilimab group, compared to a +9.8% in the placebo group.

To date, no adverse drug reactions (ADRs) for daxdilimab have been identified. 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 injection site reactions, vaccine interaction, drug-drug interactions, and reproductive toxicity.

2.2.2 Known Potential Benefits

In this Phase 2a trial, it is hypothesized that participants moderate-to-severe alopecia areata may see an improvement in their condition as a result of participating in the trial.

Participation in this trial may help generate future benefit for larger groups of patients with AA if daxdilimab proves to be successful in treating this disease.

2.2.3 Assessment of Risks and Benefits

All quality, pharmacology and toxicology data, and satisfactory safety and tolerability data demonstrated in nonclinical studies are considered sufficient to expect a positive benefit/risk ratio for the treatment of patients with moderate-to-severe AA with daxdilimab, and therefore to initiate this trial.

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

3 OBJECTIVES AND ENDPOINTS

Primary Objective	**Efficacy Endpoint**
To evaluate the effect of daxdilimab on reducing hair loss at Week 24 in participants with AA.	Percent change from baseline in SALT score at Week 24.
Secondary Objectives	**Efficacy Endpoints**
To evaluate the effect of daxdilimab on reducing hair loss through 9 months of treatment in participants with AA.	• Percent change from baseline in SALT score at Weeks 12-20; 28-36. • Proportion of participants who achieve ≥50% reduction in SALT from baseline at Weeks 12-36. • Proportion of participants with absolute SALT score ≤ 10, 20, 30, 50 at Weeks 12-36.
To evaluate the post-treatment duration effect of daxdilimab on reducing hair loss in participants with AA.	• Percent change from baseline in SALT score at Weeks 40-48. • Proportion of participants who achieve ≥50% reduction in SALT from baseline at Weeks 40-48. • Proportion of participants with absolute SALT score ≤ 10, 20, 30, 50 at Weeks 40-48.
PK/PD/Immunogenicity Objectives	**PK/PD/Immunogenicity Endpoints**
To characterize the PK, PD, and immunogenicity of daxdilimab.	• Daxdilimab concentrations. • Change from baseline in pDCs. • ADA rate.
Safety Objectives	**Safety Endpoints**
To evaluate the safety and tolerability of daxdilimab.	• Incidence of AEs, SAEs, and AESIs.

Exploratory Objectives	Efficacy Endpoints
[redacted]	• [redacted]
[redacted]	[redacted]
[redacted]	• [redacted]

Abbreviations: AA, Alopecia Areata; ADA, anti-drug antibody; AE, adverse event; AESI, adverse event of special interest; [redacted]; PD, pharmacodynamic; pDC, plasmacytoid dendritic cell; PK, pharmacokinetic; SAE, serious adverse event; SALT, Severity of Alopecia Tool.

4 TRIAL DESIGN

4.1 Overall Design

This is a Phase 2a, multicenter, open-label, proof-of-concept trial to assess the preliminary efficacy, safety, tolerability, PK, and PD of daxdilimab in participants with moderate-to-severe AA, with ≥50% and ≤95% total scalp hair loss as defined by the Severity of Alopecia Tool (SALT) score at Screening and Day 1. Participants will be between 18 and 65 years of age (inclusive), with a current episode of hair loss of >3 months but <7 years, along with investigator's assessment that hair regrowth is possible and no evidence of active regrowth present at baseline, and no known history of significant regrowth during the last 6 months. Approximately 30 participants will be enrolled to receive daxdilimab [redacted] mg administered subcutaneously [redacted].

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

The trial will comprise of a screening period of up to 30 days with enrollment on Day 1. Participants will be treated with daxdilimab [redacted] mg [redacted] The primary endpoint assessment will occur during the Week 24 visit. All participants will have a follow-up period of 16 weeks (through Week 48) to evaluate long-term safety and to observe the duration of efficacy following the treatment period. Participants who prematurely stop dosing will be followed through Week 48 unless participants withdraw consent of trial participation or are lost to follow-up. Any participant who discontinues from the trial prematurely and does not plan to participate in the post-treatment follow-up period will be requested to complete the ET visit.

For scheduled trial visits, participants will come to the trial centers on 14 occasions: screening, [redacted]

Efficacy will be evaluated by assessment of SALT scores, [redacted].

Blood samples will be collected from all participants to characterize the PK, PD, and immunogenicity of daxdilimab.

Safety will be assessed by collecting AEs, SAEs, adverse events of special interest (AESIs), performing local injection tolerability assessment, recording vital signs, performing physical examinations and electrocardiograms (ECGs), and evaluating clinical laboratory results.

4.2 Scientific Rationale for Trial Design

The proposed open label trial design is considered appropriate for assessing the preliminary efficacy, safety, tolerability, PK, PD, and immunogenicity of daxdilimab in participants with moderate-to-severe AA.

[redacted]

4.4 End of Trial Definition

A participant is considered to have completed the trial if he or she was followed through the last protocol-specified visit (Week 48 or ET), regardless of the number of doses of investigational product (IP) that were received as shown in the Schedule of Assessments, Table 1.

The end of the trial is defined as completion of the last visit or procedure shown in the Schedule of Assessments for the last enrolled participant.

5 TRIAL POPULATION

5.1 Inclusion Criteria

All participants must meet all of the following criteria to be eligible for trial participation, either at the screening and Day 1 visits, or only at one of the specified visits (screening or Day 1) as noted in the criterion:

1. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the United States,) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations.
2. Adult men and women, aged 18 to 65 years, inclusive, at the time of informed consent.
3. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial.
4. Willing to keep the same hair style and color (eg, hair products, process, and timing for hair appointments) for the duration of the trial.
5. Clinical diagnosis of moderate-to-severe AA - defined as the presence of ≥ 50% and ≤ 95% total scalp hair loss at screening and baseline (Day 1) defined by the SALT score.
6. Duration of current episode of hair loss >3 months but <7 years at screening and Day 1, along with investigators' assessment that hair regrowth is possible. Total duration since diagnosis of AA could be >7 years.
7. No evidence of active regrowth present at baseline and no known history of significant regrowth, as per investigator's judgement, over the last 6 months.
8. Female of childbearing potential must have a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1.
9. For female participant of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the participant must agree to use a highly effective contraceptive method from at least 4 weeks prior to Day 1 until at least 6 months (approximately 5 half-lives) after the last IP administration or the end of the trial, whichever is longer, and refrain from egg retrieval/egg donation during this period. Highly effective contraceptive methods include hormonal contraceptives (e.g, combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s) (provided his vasectomy was performed ≥4 months prior to Screening), tubal ligation or double barrier methods of contraception (e.g. male condom with cervical cap, male condom with diaphragm, and male condom with contraceptive sponge) in conjunction with spermicide.

   Note: For countries where double barrier methods are not accepted as highly effective contraception, this option must not be considered.

   Note: Participants must have been on a stable dose of hormonal contraceptives for at least 4 weeks before Day 1.

   Note: The above list of contraceptive methods does not apply to participants who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal intercourse throughout the trial and for at least 6 months after the last IP administration or until

the end of the trial, whichever is longer. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not acceptable.

Note: A female participant of nonchildbearing potential is defined as follows:

- Female participant who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy).
- Female participant who has had a cessation of menses for at least 12 months prior to the screening visit without an alternative medical cause, and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels).

10. For male participant involved in any sexual intercourse that could lead to pregnancy, participant must agree to use one of the highly effective contraceptive methods listed in Inclusion Criterion #9, from Day 1 until at least 6 months (approximately 5 half-lives) after the last IP administration and refrain from donating sperm during this period. If the female partner of a male participant uses any of the hormonal contraceptive methods listed above, this contraceptive method should be used by the female partner from at least 4 weeks before Day 1 until at least 6 months after the last administration of daxdilimab.

5.2 Exclusion Criteria

Participants will be ineligible for trial participation if they meet any of the following criteria at the Screening and/or Day 1 visits, as applicable:

General Exclusion Criteria

1. Individuals involved in the conduct of the trial, their employees, or immediate family members of such individuals.

2. Any clinically significant medical condition or physical/laboratory/ECG/vital signs abnormality that would, in the opinion of the investigator, put the participant at undue risk or interfere with the evaluation of the IP or interpretation of trial results.

3. History of allergy, hypersensitivity reaction, or anaphylaxis to any component of the IP or to a previous mAb or Ig therapy.

4. Participant has had excessive sun exposure, is planning a trip to a sunny climate, or has used tanning booths within 4 weeks prior to Day 1 or is not willing to minimize natural and artificial sunlight exposure during the trial. Use of sunscreen products and protective apparel are recommended when sun exposure cannot be avoided.

5. Spontaneous or induced abortion or still or live birth $\leq$ 4 weeks prior to Screening.

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 or until the end of the trial, whichever is longer.

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 trial assessments.

8. Major surgery within 8 weeks prior to Screening or elective surgery planned during the trial.

9. Known history of a primary immunodeficiency or an underlying condition such as known human immunodeficiency virus (HIV) infection, a positive result for HIV infection, splenectomy, or any underlying condition that in the opinion of the investigator significantly predisposes the participant to infection.

10. At Screening, any of the following (tests may be repeated once within the same Screening period to confirm results prior to Day 1):

    - Aspartate aminotransferase (AST) > 2.5× upper limit of normal (ULN)
    - Alanine aminotransferase (ALT) > 2.5× ULN
    - Total bilirubin > 1.5× ULN (unless due to Gilbert's syndrome)
    - Serum immunoglobulin G (IgG) < 600 mg/dL (or < 6 g/L)
    - Neutrophil count < 1000/µL (or < 1.0×10^9/L)
    - Platelet count < 50,000/µL (or < 50×10^9/L)
    - Hemoglobin < 8 g/dL (or < 80 g/L)
    - Total lymphocyte count < 200 cells/mm^3
    - Glomerular filtration rate (Modification of Diet in Renal Disease [MDRD]) < 30 mL/min/1.73 m^2
    - Spot urine protein to creatinine ratio (UPCr) > 3 mg/mg

11. Confirmed positive test for hepatitis B serology defined as:

    - Hepatitis B surface antigen (HBsAg), or
    - Hepatitis B core antibody (HBcAb or anti-HBc)

12. Positive test for hepatitis C virus antibody.

13. Active tuberculosis (TB), or a positive TB test at Screening. Participant will be evaluated for latent TB infection with a purified protein derivative (PPD) test or a QuantiFERON-TB Gold test. Participants who demonstrate evidence of latent TB infection (either PPD ≥5 mm of induration or positive QuantiFERON-TB Gold test, irrespective of bacille Calmette-Guérin vaccination status will not be allowed to participate in the trial, unless documented history of appropriate treatment for active or latent TB. Participants with an indeterminate test result can repeat the test, but if the repeat test is also indeterminate, they are excluded.

14. Any severe herpes virus family infection (including Epstein-Barr virus, cytomegalovirus [CMV]) at any time prior to Day 1, 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.

15. Any herpes zoster, CMV, or Epstein-Barr virus infection that was not completely resolved 12 weeks prior to Day 1.

16. Any of the following within 30 days prior to signing the ICF and though Day 1:

- Clinically significant active infection in the opinion of the investigator, including ongoing, and chronic infection requiring antibiotics or antiviral medication (chronic nail infections are allowed). Note: Participant with a limited recurrence of a cold sore or herpes genitalis between ICF signature and Day 1 could be eligible based on the investigator's judgement.
- Any infection requiring hospitalization or treatment with intravenous (IV) anti-infectives.
- A participant with a documented positive severe acute respiratory syndrome coronavirus 2 (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 resolution of symptomatic Coronavirus Disease 2019 (COVID-19) illness.

17. Opportunistic infection requiring hospitalization or parenteral antimicrobial treatment within 2 years prior to Day 1.

18. Any acute illness or evidence of clinically significant active infection, such as fever ≥ 38.0°C (≥ 100.5°F) on Day 1.

19. History of clinically significant cardiac disease including unstable angina; myocardial infarction within 6 months prior to Day 1; congestive heart failure; arrhythmia requiring active therapy, except for clinically insignificant extra systoles, or minor conduction abnormalities; or presence of clinically significant abnormality on ECG if, in the opinion of the investigator, it would increase the risk of trial participation.

20. History of cancer or lymphoproliferative disease within 5 years prior to Day 1, except as follows:

    - In situ carcinoma of the cervix treated with apparent success with curative therapy > 12 months prior to Screening, or
    - Nonmetastatic cutaneous basal cell or squamous cell carcinoma of the skin treated with apparent success with curative therapy.

21. Receipt of a live or live-attenuated vaccine within 8 weeks prior to Day 1 or plans to receive a live or live attenuated vaccine during the trial and up to 4 weeks after the last IP administration.

22. Nonlive and nonlive-attenuated vaccines for COVID-19 (eg, RNA-based vaccines, protein-based vaccines, and nonreplicating viral vector-based vaccines) are not allowed within 4 weeks prior to Day 1 and within 2 weeks prior to each trial visit.

23. Participant should be assessed for epidemiologic risk of COVID-19 (ie, recent exposure, high-risk housing) and for health-related risk of COVID-19 severity based on current understanding of risk factors for severe disease when making a decision regarding the individual's risk of participation. 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 enrolled.

24. 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 trial or at a blood bank donation), or plans to give blood or plasma during their participation in the trial or up to 6 months after the last IP administration, whichever is longer.

25. Transfusion with blood, packed red blood cells, platelets or treatment with plasmapheresis, or plasma exchange within 8 weeks prior to Day 1 and for the total duration of the trial participation.

Disease-related Criteria

26. Active forms of other inflammatory skin disease(s) or evidence of other skin conditions (eg, psoriasis, seborrheic dermatitis, lupus) at the time of the Screening and through Day 1, that in the opinion of the investigator might interfere with evaluation of AA and the assessment of the activity measures.

27. Presence of another form of alopecia (except for androgenic alopecia).

28. History of male or female pattern hair loss > Hamilton stage III or > Ludwig stage II.

29. History or presence of hair transplants.

30. History or presence of micropigmentation of the scalp (Note: microblading of the eyebrows is permitted).

Prior and concomitant Therapy Criteria

31. Use of steroids (systemic and intralesional), anthralin, squaric acid, diphenylcycloprophenone (DPCP), dinitrochlorobenzene (DCNB), protopic, minoxidil, or any other medication which in the opinion of the investigator may affect hair regrowth within 4 weeks of Day 1 visit.

    Note: Intranasal and inhaled corticosteroids are allowed, eye and ear drops containing corticosteroids are also allowed.

32. Use of platelet-rich plasma injections in the last 12 weeks prior to Day 1.

33. Topical medicated treatment that could affect AA including, but not limited to, topical corticosteroids, calcineurin inhibitors, antimicrobials, medical devices within 2 weeks of Day 1 visit.

    Note: Topical corticosteroids are permitted outside of the scalp, eyebrows, and eyelids.

34. Participants who have had previous treatment with any biologic B-cell-depleting therapy (eg, rituximab, ocrelizumab, or ofatumumab) or other B-cell targeting therapy (eg, belimumab) within 12 months before Day 1.

35. Participants who have received previous treatment with pDC inhibiting therapies (eg, anti-ILT7, anti-blood dendritic cell antigen 2 [BDCA2]).

36. Inadequate response to adequate trial of oral Janus Kinase (JAK) inhibitors. Previous exposure to topical JAK inhibitors is acceptable, regardless of response.

37. Any biologic or conventional disease-modifying antirheumatic drugs (DMARD), immunosuppressant (eg, cyclosporine, methotrexate, or azathioprine), JAK-inhibitors, interferon (IFN) blocking therapies, or antiproliferative agents, if last dose was taken:

a. within 8 weeks prior to Day 1 or

b. drug-specific 5 half-lives elimination period (if longer than 8 weeks).

38. Participant has received any marketed or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.

39. Currently receiving a nonbiological IP or device or has received one within 4 weeks prior to Day 1 or within 5 published half-lives, whichever is longer.

40. Participant has received any ultraviolet (UV)-B phototherapy (including tanning beds), has had psoralen-UV-A (PUVA) treatment, or excimer laser within 4 weeks prior to Day 1.

5.3 Lifestyle Considerations

Participants are expected to continue their usual scalp care routine without notable changes for the course of the treatment periods and follow-up period. Participants are prohibited from using tanning booths and sunbathing during the trial, and from shaving their scalp 2 weeks prior to visits. Participants are to keep the same hair style and color (eg, hair products, process, and timing for hair appointments) for the duration of the trial.

5.4 Screen Failures

Screen failures are defined as individuals who consent to participate in the clinical trial but are not subsequently enrolled in the trial. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened once, if deemed acceptable by the investigator. Rescreened participants should be assigned a different participant number than the initial screening. All procedures planned at the screening visit, including signature of a new consent form, will be performed.

6 TREATMENT

6.1 Trial Treatment Administered

This trial involves SC administration of daxdilimab [redacted] mg (two 1.5 mL injections) [redacted]. The IP will be administered by trial site staff in the clinic. On Day 1 and [redacted] participants will remain under observation for at least 1 hour after IP administration. The IP will be provided by the sponsor. Further details regarding the IP can be found in Table 2.

Table 2: Trial Treatment

	Investigational Product
Product name	Daxdilimab
Dosage form	[redacted]
Source of procurement	Horizon Therapeutics
Unit dose strength(s)/Dosage level(s)	[redacted] mg dose, administered as 2 x 1.5 mL SC injections.
Route of Administration	Subcutaneous, [redacted] (total of 9 doses)
Physical description	[redacted]
Dosing instructions	Daxdilimab should be administered by clinic staff trained in best practices for SC administration of treatments. More details on the administration method are described in the study manual.

Abbreviations: [redacted]; SC, subcutaneous.

The contents of the label will be in accordance with all applicable regulatory requirements.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Preparation/Storage/Handling

The IP must be stored in a secure environmentally controlled and monitored area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff. The IP may only be supplied by authorized site staff and may only be given to participants enrolled into the trial.

Daxdilimab vials must be refrigerated at 2-8° C (36°F to 46°F) until the day of use.

Investigational product will be dispensed by the trial site only for administration to trial participants.

6.2.2 Accountability

The investigator is responsible for maintaining accurate records of the IP received initially and of the trial product dispensed/used. Any IP accidentally or deliberately destroyed, or returned to the sponsor or designee will be accounted for. Any discrepancies between amounts dispensed and returned will be explained. At the conclusion of the trial, all used and unused IPs and all medication

containers should be reconciled and either destroyed on site or returned, as requested by the Sponsor.

All IP accountability forms and treatment logs must be retained in the investigator's study files. Product inventory and accountability records will be maintained, as per International Council for Harmonisation (ICH) Good Clinical Practice (GCP). These records must be available for inspection at any time by the sponsor, its designees, or by regulatory agencies.

Further guidance and information for final disposition of IPs are provided in the study manual.

6.3 Randomization

At the trial site, each screened participant will be assigned a participant identifier number during screening that will be used on all participant documentation. The participant identifier number will contain the country ID, site number, and the participant number, and will be assigned in numerical order at the screening visit based on chronological order of screening dates (e.g., US-002-010 for the 10th participant screened at Site #002 in the United States).

No randomization scheme will be used, as all participants will receive the active IP only.

6.3.1 Blinding

This is an open-label trial. Participants and investigators are aware that the IP is daxdilimab.

6.3.2 Trial Treatment Compliance

Trial treatment compliance in this trial will be under the direct control of the investigator; the IP will always be administered on site. The date and time of each dose administered in the clinic will be recorded.

6.4 Concomitant Therapy

All medications (including over-the-counter drugs, vitamins, herbal/natural products, and antacids) taken within 4 weeks prior to screening and throughout the trial must be recorded. In addition, the use of any prohibited medications must be recorded within the timeframe described in the exclusion criteria. No rescue medications or treatments are permitted in this study.

Medication entries may be captured as generic or trade names. Trade names should be used for combination drugs. Entries should include as much as possible of the following information: the dose, unit, frequency of administration, route of administration, start date, end date, and indication. If the medication is stopped or the dosage is changed, these details must be recorded.

6.4.1 Permitted Therapies

The following therapies are permitted:

- Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.

- Use of sunscreen products and protective apparel are permitted when sun exposure cannot be avoided.
- Topical corticosteroids are permitted outside of the scalp, eyebrows, and eyelids.
- Nonlive and nonlive-attenuated vaccines for COVID-19 (eg, RNA-based vaccines, protein-based vaccines, and nonreplicating viral vector-based vaccines) are allowed > 4 weeks prior to Day 1 and > 2 weeks prior to each trial visit.

6.4.2 Prohibited Therapies or Procedures

Participants who start prohibited medications or therapies that have been demonstrated to be effective for treatment of AA during the trial will be withdrawn from trial treatment. Participants who start prohibited medications or therapies for other reasons during the trial may be withdrawn from trial 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 3 lists prohibited medications that are not to be used from the defined washout periods before the first administration of trial treatment at the Day 1 visit through the last trial visit.

Table 3: Prohibited Therapies or Procedures

Prohibited medications, products, and procedures	Washout period prior to first dose (Day 1)
Any pDC inhibiting therapies (eg, anti-ILT7, anti-BDCA2).	Lifetime
History or presence of hair transplants.	Lifetime
Micropigmentation of the scalp (Note: microblading of the eyebrows is permitted).	Lifetime
Any biologic B-cell-depleting therapy (eg, rituximab, ocrelizumab, or ofatumumab) or other B-cell targeting therapy (eg, belimumab).	12 months
Any marketed or investigational biological agent.	12 weeks or 5 half-lives, whichever is longer
Platelet-rich plasma injections.	12 weeks
Transfusion with blood products, packed red blood cells, platelets or treatment with plasmapheresis, or plasma exchange.	8 weeks
Any biologic or conventional DMARD, immunosuppressant (eg, cyclosporine, methotrexate, or azathioprine), JAK-inhibitor, IFN blocking therapies, or antiproliferative agents.	8 weeks or 5 half-lives whichever is longer
Live and live attenuated vaccines.	8 weeks

Prohibited medications, products, and procedures	**Washout period prior to first dose (Day 1)**
Nonbiological investigational product or device.	4 weeks or 5 published half-lives, whichever is longer
Nonlive and nonlive-attenuated vaccines for COVID-19 (eg, RNA-based vaccines, protein-based vaccines, and nonreplicating viral vector-based vaccines).	4 weeks prior to Day 1 and within 2 weeks prior to each trial visit
PUVA treatment, UV-B phototherapy (including tanning beds) or excimer laser, excessive sun exposure or has used tanning booths.	4 weeks
Steroids (systemic and intralesional), anthralin, squaric acid, DPCP, DCNB, protopic, minoxidil, or any other medication which in the opinion of the investigator may affect hair regrowth. Note: Intranasal and inhaled corticosteroids are allowed, eye and ear drops containing corticosteroids are also allowed.	4 weeks
Topical medicated treatment that could affect AA including, but not limited to, topical corticosteroids, calcineurin inhibitors, antimicrobials, medical devices. Note: Topical corticosteroids are permitted outside of the scalp, eyebrows, and eyelids.	2 weeks

Abbreviations: AA, alopecia areata; BDCA2, blood dendritic cell antigen 2; DCNB, dinitrochlorobenzene; DPCP, diphenylcycloprophenone; DMARD, disease-modifying antirheumatic drug; IFN, interferon; ILT7, immunoglobulin-like transcript 7; IVIg, intravenous immunoglobulin; JAK, Janus Kinase; pDC, plasmacytoid dendritic cell; PUVA, psoralen and ultraviolet A; UV, ultraviolet.

7 DISCONTINUATION AND LOST TO FOLLOW-UP

Participants have the right to withdraw from the trial at any time for any reason without penalty. The investigator also has the right to withdraw participants from treatment if he or she feels it is in the best interest of the participant or if the participant is uncooperative or noncompliant.

Should a participant decide to withdraw and does not plan to participate in the post-treatment follow-up period, all efforts will be made to complete and report the observations as thoroughly as possible, particularly the examinations outlined in the ET visit.

The investigator or one of his or her staff members should contact the participant to determine as accurately as possible the primary reason for the withdrawal.

A complete final evaluation at the time of the participant's withdrawal should be made with an explanation of why the participant is withdrawing from the trial. If the reason for removal of a participant is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded.

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

7.1 Discontinuation

Any participant who decides to discontinue from the trial prematurely and does not plan to participate in the post-treatment follow-up period will be requested to complete the ET visit.

Participants who discontinue will not be replaced.

7.1.1 Discontinuation of Investigational Product

An individual participant will not receive any further IP if any of the following occur in the participant:

- Receipt of any medications that have been demonstrated to be effective for treatment of AA as described in Section 6.4.2.
- A CTCAE Grade 3 or higher allergic reaction to the IP.
- A CTCAE Grade 3 or higher infection considered related to the IP.
- Other AE that contraindicates further dosing in the opinion of the investigator and/or the Sponsor, or Medical Monitor.
- Withdrawal of consent from further treatment with IP.
- Participant is determined to have met one or more of the exclusion criteria or failed to meet all the inclusion criteria for study participation and there is a potential safety risk associated with continuation identified upon consultation with the Medical Monitor.
- Pregnancy or a decision to become pregnant.
- Any of the following liver function abnormalities:
  - ALT or AST ≥ 8× ULN.

- ALT or AST ≥ 5× ULN for more than 2 weeks.
- ALT or AST ≥ 3× ULN and total bilirubin ≥ 2× ULN.
- ALT or AST ≥ 3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (≥ 5%).

Participants who are permanently discontinued from receiving IP will be followed for protocol-specified assessments including follow-up of any AEs through Week 48 unless consent is withdrawn specifically from further trial participation (Section 7.1.3), or the participant is lost to follow-up (Section 7.2). Site investigators will be trained about the importance of retention of participants through the completion of the study, and participants will be informed about the continued scientific importance of their data even if they discontinue study treatment early.

7.1.2 Discontinuation from the Trial

Reasons for discontinuation from the trial include the following:

- The participant is lost to follow-up.
- The sponsor or regulatory authorities, for any reason, stop the trial. In this case, all participants will be discontinued from the trial. The investigator will immediately, on discontinuance of the trial by the sponsor, in its entirety or at a clinical trial site, inform both the participants and the research ethics board of the discontinuance, provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of participants or other persons.

7.1.3 Withdrawal of Consent from the Trial

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. If a participant withdraws participation in the study, then no further study visits or data collection should take place. Further details concerning use of samples collected during the study from a participant who withdraws consent are provided in Section 10.9.

7.2 Lost to Follow-Up

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

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

- The site will attempt to contact the participant and reschedule the missed visit. The site will then counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to or should continue in the trial.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, three 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 or trial file.

- If all attempts to contact the participant fail, he or she will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

8 TRIAL ASSESSMENTS AND PROCEDURES

8.1 Efficacy Assessments

Clinical evaluations of AA will be performed by an experienced and qualified dermatologist (board certified or equivalent) or other suitably qualified and experienced designee. To assure consistency and reduce variability, the same assessor should perform all assessments on a given participant whenever possible.

8.1.1 Severity of Alopecia Tool (SALT)

To participate in this trial, a participant must have moderate-to-severe AA as assessed by a SALT score of ≥ 50 and ≤ 95 at screening and baseline (Day 1) as described in Section 5.1.

The SALT score is a well-validated metric and widely utilized tool for determining the degree of hair loss based on the percentage of scalp surface area involved on the top, back, and each side of the scalp for AA. The investigator will determine the percent scalp hair loss in a given quadrant, multiply this by the total scalp area delineated by that quadrant, and sum the resultant numbers for each quadrant to give the total percent scalp hair loss with a maximum score of 100.[21] The SALT assessment tool is provided in Appendix 1.

8.1.2 [redacted]

[redacted]

8.1.3 [redacted]

[redacted]

8.1.4 Medical Photography

Medical photographs of the full scalp for all participants, and of the eyebrows and eyelashes for participants who have hair loss in these areas at baseline, will be performed at the visits specified in Table 1. Care will be taken to use the same camera, the same magnification, and the same settings for each photograph at each visit in order to obtain comparable pictures.

Additional information for the medical photograph will be provided in the corresponding study manual.

8.2 Pharmacokinetics

Blood samples will be collected for analysis of daxdilimab concentrations for all participants who received ≥ 1 dose of IP 2 hours (±5 minutes) after dosing on Day 1 and pre-dose at all other visits specified in Table 1.

The actual date and time of each blood sample collection will be recorded in the electronic case report form (eCRF).

Details about the collection, processing, handling, storage, and shipping of PK samples will be provided in the laboratory manual.

8.3 Pharmacodynamics

Blood samples will be collected for [redacted] of daxdilimab at the visits and timepoints specified in Table 1. [redacted]

The actual date and time of each blood sample collection will be recorded in the eCRF.

Details about the collection (including blood volume required for each sample collection), processing, handling, storage, and shipping of PD samples will be provided in the laboratory manual.

8.4 Immunogenicity

Blood samples will be collected for analysis of serum daxdilimab ADA.

The actual date and time of blood sample collection will be recorded in the eCRF.

Details about the collection (including blood volume required for sample collection), processing, handling, storage, and shipping will be provided in the laboratory manual.

8.5 Safety and Other Assessments

8.5.1 Vital Signs

The following vital signs will be recorded at the visits specified in Table 1 with the participant in a seated or supine position, after having sat calmly for at least 5 minutes: systolic and diastolic blood pressure (mmHg), pulse (bpm), body temperature (°C), and respiratory rate (breaths/minute).

Weight (kg) and height (cm) will be collected to calculate the BMI, and will be recorded at the visits specified in Table 1. The height will only be recorded once at the screening visit and the same value will be used for BMI calculation at other visits.

If deemed appropriate by the investigator, clinically significant findings in the vital signs will exclude a participant from trial participation. Any abnormal finding related to vital signs that the investigator considers to be clinically significant must be recorded as an AE.

8.5.2 Physical Examination

The following sites/systems will at least be included in the focused physical examination, which will be performed at the visits specified in Table 1:

- General appearance
- Dermatological (except AA)
- Head, eyes, ears, nose, throat (HEENT)
- Respiratory
- Cardiovascular
- Abdominal
- Neurological
- Musculoskeletal
- Lymphatic

Information for all physical examinations must be included in the source document. If deemed appropriate by the investigator, clinically significant findings in the physical examination will exclude a participant from trial participation. Any significant change will be reported as an AE in the source document and eCRF.

8.5.3 Clinical Laboratory Tests

Laboratory tests will be performed at the visits specified in Table 1. The tests will include urinalysis, hematology with differential, a standard chemistry panel (chemistry includes liver function tests), and serum pregnancy test (screening) for women of childbearing potential (WOCBP). At the visit specified in Table 1, a urine pregnancy test will be performed for WOCBP (conducted at the investigator site). The specific tests in these panels are listed in Table 4.

Table 4: Clinical Laboratory Testing

Laboratory Testing	Tests Included
Hematology	HCT, Hg, MCH, MCHC, MCV, MPV, PLT, RBC, WBC, and differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils relative and absolute)
Biochemistry	Albumin, alkaline phosphatase, ALT, AST, bicarbonate, calcium, chloride, creatinine (enzymatic), GGT, glomerular filtration rate (MDRD), glucose random, LDH, magnesium, potassium, sodium, total bilirubin (including direct and indirect), triglycerides, urea (BUN), uric acid
Urinalysis	Dipstick and microscopic analysis (as required) Spot UPCr
Urine pregnancy test	For female participants of childbearing potential (at each visit, except screening)
Laboratory tests required at screening only	FSH levels for female participants who have had a cessation of menses for at least 12 months prior to the screening visit without an alternative medical cause Serum IgG (screening). β-hCG for women of childbearing potential (screening) Tuberculosis test (PPD or QuantiFERON-TB Gold) Serology (HBV [HBsAg, HBcAb or anti-HBc], HCV, HIV)

Abbreviations: ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; AST, aspartate aminotransferase; β-hCG, β-human chorionic gonadotropin; BUN, blood urea nitrogen; FSH, follicle-stimulating hormone; GGT, gamma-glutamyl-transferase; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigens; HBV, hepatitis B virus; HBcAb, hepatitis B core antibody; HCT, hematocrit; HCV, hepatitis C virus; Hgb, hemoglobin; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MDRD, Modification of Diet in Renal Disease; MPV, mean platelet volume; PLT, platelets; PPD, purified protein derivative; RBC, red blood cell (count); UPCr, urine protein to creatinine ratio; WBC, white blood cell (count).

In case of a screening laboratory value abnormality, the test can be repeated once within the original screening time window, if the investigator believes there is a reasonable possibility that the participant would be eligible if re-tested.

If deemed appropriate by the investigator, clinically significant findings in clinical laboratory testing will exclude a participant from trial participation. Any clinically significant value will be reported as an AE.

8.5.4 Electrocardiogram

Twelve-lead ECGs will be performed as a safety assessment at the visits specified in Table 1. Clinically significant findings in the ECG should exclude a participant from trial participation (as

deemed appropriate by the investigator). Any clinically significant value will be reported as an AE.

8.5.5 Local Injection Tolerability Assessments

Assessor local injection tolerability assessments will be performed approximately 30 minutes post-dose (can be performed any time at Week 36 as no IP is administered), at the visits specified in Table 1. The investigator, or designee, will evaluate the injection sites at these visits, and will 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 36 can be performed for any ongoing injection site reactions.

8.6Adverse Events and Serious Adverse Events

8.6.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not considered related to the IP.

8.6.2 Definition of Treatment-Emergent Adverse Event

A TEAE is any condition that was not present prior to treatment with the IP but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated).

8.6.3 Definition of Serious Adverse Event

A SAE or reaction is any untoward medical occurrence that, at any dose has any of the following consequences:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Note: 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 that hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether expedited 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 intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.6.4 Definition of an Adverse Event of Special Interest (AESI)

An AESI is an AE of scientific and medical interest specific to understanding of the IP and may require close monitoring and collection of additional information by the investigator. An AESI may be serious or nonserious.

The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this IP.

The following AESIs will be particularly monitored in this trial:

- Hypersensitivity reaction, including anaphylaxis.
- Severe viral infection/reactivation (CTCAE Grade 3 or higher).
- Opportunistic infection.
- Malignancy (except non-melanoma skin cancer).

8.6.5 Classification of an Adverse Event

8.6.5.1 Relationship to Trial Treatment

The investigator is required to provide an assessment of the relationship of AEs and SAEs to the IP. An event will be considered "not related" to use of IP if any of the following are met:

- An unreasonable temporal relationship between administration of the IP and the onset of the event (eg, the event occurred either before, or too long after, administration of the IP for it to be considered IP related).
- A causal relationship between the IP and the event is biologically implausible (eg, death as a passenger in an automobile accident).
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event).

Individual AE/SAE reports will be considered "related" to use of the IP if the "not related" criteria are not met.

"Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the IP (ie, there are facts, evidence, or arguments to suggest possible causation).

8.6.5.2 Adverse Event Severity

The guidelines outlined in CTCAE v5.0 will be used for assessing the severity or intensity of the

event. The general guidelines for assessing the AE grade are provided in Table 5.

Table 5: CTCAE v5.0 General Guidelines

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL [a].
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL [b].
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Abbreviations: ADL, activities of daily living; AE, adverse event; CTCAE, Common Terminology for Adverse Events.
The CTCAE v5.0 is dated to 27 NOV 2017.
[a] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.6.5.3 Expectedness

Horizon Therapeutics Ireland DAC will assess the expectedness of each SAE in relation to the IP.

8.6.6 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of trial personnel during trial visits and interviews of a trial participant presenting for medical care, or upon review by a trial monitor.

All AEs, including local and systemic reactions, will be captured on the appropriate eCRF. Information to be collected includes event description, date of onset, clinician's assessment of severity, relationship to IP (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs occurring while on trial must be documented appropriately regardless of relationship.

Trial site personnel will note the occurrence and nature of each participant's medical condition(s) present prior to the informed consent signature in the appropriate section of the source document and eCRF. During the trial, site personnel will note any change in the condition(s) and the occurrence and nature of any AE.

Any medical condition that is present prior to informed consent signature will be considered as part of medical history and not reported as an AE. However, if the trial participant's condition deteriorates after the consent signature, it will be recorded as an AE.

Should a participant experience an AE at any time after the informed consent signature until the end of participation in the trial, the event will be recorded as an AE in the source document and eCRF. Any SAE related to the trial participation (e.g., screening procedure) will be recorded in

the source document and eCRF from the time consent is given to participate in the trial until the end of participation in the trial.

The investigator is responsible for appropriate medical care of participants during the trial. The investigator also remains responsible for following through with an appropriate health care option for all AEs that are ongoing at the end of the trial. The participant should be followed until the event is resolved or stable. If an AE is ongoing at the end of trial, the follow-up duration is left to the discretion of the investigator. Follow-up frequency will be performed at the discretion of the investigator.

Whenever possible, clinically significant abnormal laboratory results are to be reported using the diagnostic that resulted in the clinically significant abnormal laboratory results and not the actual abnormal test.

8.6.7 Adverse Event Reporting

Investigators are responsible for monitoring the safety of participants who are participating in this trial and for alerting the sponsor to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

8.6.8 Serious Adverse Event Reporting

Horizon Therapeutics Ireland DAC will be the pharmacovigilance unit responsible for the overall pharmacovigilance process for this trial. All SAEs, related to the experimental treatment or not, occurring during the course of the trial must be reported by entering the information into the eCRF within 24 hours of knowledge of the occurrence (this refers to any AE that meets one or more of the aforementioned serious criteria). The SAE reporting period ends at the end of the follow-up period or if the participant begins an alternative therapy.

If unable to access the eCRF, the event must be reported by submitting the completed SAE form to the following e-mail address (faxing can also be done as a second option in case e-mailing is not possible) within 24 hours after becoming aware that a participant has experienced an SAE.

Safety Contact Information: Horizon Therapeutics
E-mail: clinicalsafety@horizontherapeutics.com
US Fax: (800) 860-7836

The pharmacovigilance unit will inform the medical monitor, the sponsor, and Innovaderm within 1 business day of awareness of a new SAE. The pharmacovigilance unit will process and evaluate all SAEs as soon as the reports are received. For each SAE received, the pharmacovigilance unit, in consultation with the Sponsor if needed, will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met.

The expedited reporting of relevant safety information to concerned regulatory agencies and ethic committees will be performed in accordance with local laws and regulations and will be defined in the Safety Management Plan.

The trial sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reactions as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify the FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

8.6.9 Pregnancy Reporting

If a female participant becomes pregnant during the trial or up to 6 months after the last IP administration, whichever is longer, the participant should inform the trial site as soon as possible. Upon confirmation of the pregnancy, the female participant will be discontinued from the trial. If a female partner of a male participant becomes pregnant up to 6 months after the last IP administration of the male subject, the participant should inform the trial site as soon as possible. The investigator must complete a trial-specific pregnancy form upon confirmation of a pregnancy and send it to the pharmacovigilance unit within 24 hours of confirmation of the pregnancy (contact information to be used is the same as for SAE reporting). The pharmacovigilance unit will report all cases of pregnancy to the medical monitor, the sponsor, and Innovaderm in a timely manner. Pregnancy is not itself an AE or SAE; however, maternal/fetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate. The investigator will follow the pregnancy until completion or until pregnancy termination and, in the case of a live-born offspring, to 1 month of age in that infant. The investigator will notify the pharmacovigilance unit and Innovaderm of the outcome as a follow-up to the initial pregnancy form. All pregnancies should be reported to the sponsor and, when applicable, to the ethics committee.

8.6.10 Overdose

Investigational product overdose is any accidental or intentional use of IP in an amount higher than the dose indicated per protocol for a given participant. Trial treatment compliance (see Section 6.3.2) should be reviewed to detect potential instances of overdose (intentional or accidental).

Any IP overdose during the trial should be recorded on the source document and eCRF. In the event of overdose, the participant should be closely monitored for any potential AEs. All AEs associated with an overdose should be entered on the Adverse Event eCRF and reported using the procedures detailed in Section 8.6.8, Serious Adverse Events Reporting, 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 non-serious on the form and the Adverse Event eCRF. The excess quantity and duration of the overdose should be recorded.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

A total of up to 30 participants will receive daxdilimab in the trial. The sample size was determined by the need to evaluate potential efficacy, safety and tolerability, and PK/PD. No formal power calculation was performed.

The mean percent reduction from baseline in SALT score was 58% in 4 mg group at Week 36 in Eli Lilly's phase 2 AA trial (n=28)[25]. The lower bound of the 95% confidence interval was about 42%. With 30 participants, if we observe a mean percent reduction from baseline in SALT score of 58% at Week 24, there is about 98% confidence that the mean percent reduction from baseline is at least 42%. The estimated probability that true mean percent reduction from baseline in SALT score is above a cutoff for an observed mean is provided in Table 6.

Table 6: Probability that true mean percent reduction from baseline in SALT score is above a cutoff for an observed mean.

	Observed	Probability that mean is		
n	Mean %reduction	≥35%	**≥42%**	≥45%
30	50%	0.97	**0.85**	0.74
	55%	>0.99	**0.95**	0.90
	58%	>0.99	**0.98**	0.95

The proportion of patients achieving SALT ≤20 at Week 36 in 4 mg group was 33% and 35% in two Eli Lilly's phase 3 AA trials. The lower bound of the 95% confidence interval was about 27%. The estimated probability that true proportion of participants achieving SALT ≤20 is above 27% and other cutoffs for an observed response rate is provided in Table 7.

Table 7: Probability that true proportion of participants achieving SALT ≤20 is above a cutoff for an observed response rate.

	Observed	Probability that response rate is		
n	response rate	≥20%	≥25%	**≥27%**
30	9 (30%)	0.87	0.67	**0.58**
	11(36.7%)	0.97	0.89	**0.84**
	12(40%)	0.99	0.95	**0.92**
	13(43.3%)	0.99	0.98	**0.96**
	15(50%)	0.99	0.99	**0.99**

9.2 Populations for Analyses

Safety analysis set: The safety analysis set is defined as participants who received any dose of daxdilimab. The efficacy, safety, PD and immunogenicity analyses will be based on the safety analysis set.

PK analysis set: The PK analysis set is defined as participants who received any dose of daxdilimab and have at least 1 measurable PK concentration post dose. The PK analyses will be based on PK analysis set.

9.3 Statistical Analyses

9.3.1 General Approach

Continuous variables will be summarized in tables and will include the number of participants, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be presented in tables as frequencies and percentages. Details of the statistical analysis will be specified in a separate statistical analysis plan (SAP).

9.3.2 Efficacy Analyses

9.3.2.1 Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint of percent change from baseline in SALT score at Week 24 will be summarized using descriptive statistics. A 2-sided 95% confidence interval will be calculated for the mean.

9.3.2.2 Analysis of the Secondary Efficacy Endpoints

The continuous secondary efficacy endpoints will be summarized similarly to the primary efficacy endpoint. The binary secondary efficacy endpoints will be summarized descriptively using frequencies and percentages. A 2-sided 95% confidence interval will be calculated for the percentage.

9.3.2.3 Handling Plan for Prohibited Medication Use

For participants who take prohibited medications that are considered to be effective for treatment of AA, the result after administration of the prohibited medications will be imputed using the worst observation, including baseline for continuous endpoints. The participants will be considered non-responder after administration of the prohibited medications for binary endpoints.

9.3.2.4 Handling Plan for Treatment discontinuation

Participants who discontinue treatment early will be asked to come to scheduled evaluations until the end of the study unless participants withdraw consent of trial participation or are lost to follow-up. The data collected after discontinuation of study treatment will be included in the analysis.

9.3.2.5 Handling Plan for Missing Data

Missing visits, due to skipped visits or early dropout of study, will have the last observation carried forward for continuous endpoints. The participants will be considered non-responders after early dropout of study for binary endpoints.

9.3.3 Safety Analyses

AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). Treatment emergent AEs will be summarized by the number of participants reporting the events, as well as by System Organ Class (SOC), Preferred Term (PT), severity, seriousness, and relationship to IP. For the summary of AEs by severity, each participant will be counted only once within a System Organ Class or a Preferred Term by using the AEs with the highest intensity within each category. For the summary of AEs by relationship to IP, each participant will be counted only once within a SOC or a PT by using the AEs with the greatest reported relationship within each category. The number and percentage of participants reporting treatment-emergent SAEs and treatment-emergent AESIs will also be summarized.

Clinically significant changes in laboratory analyses, vital signs, ECGs, and new findings on physical examination will be recorded as AEs or SAEs. Laboratory assessments, vital signs, and ECGs, as well as their changes from Baseline at each visit will also be summarized descriptively.

Concomitant medications will be coded with the World Health Organization-Drug Dictionary (WHO-DD). The number and percentage of participants who receive concomitant medications will be summarized by WHO-DD Anatomical Therapeutic Chemical category and PT. At each level of summarization, a participant is counted once if he/she reports one or more medications at that level.

9.3.4 Pharmacokinetic Analyses

Serum concentrations will be summarized descriptively by visit.

Individual serum concentration vs. actual time profiles for each participant, as well as the mean (±SD) serum concentration versus scheduled time profiles, will be presented graphically.

9.3.5 Pharmacodynamic/Immunogenicity Analyses

Descriptive summaries will be presented by visit for changes in pDC levels and ADA rate will be summarized descriptively.

9.3.6 Exploratory Analyses

The exploratory analyses will be detailed in the SAP.

9.3.7 Planned Analyses

The primary analysis will be performed when the last participant has completed Week 24 or withdraws prior to the scheduled Week 24 visit. All available data at the time of the data cut-off (including data collected after Week 24) will be included in the primary analysis.

The final analysis will be performed when all participants have completed trial.

10 REGULATORY, ETHICAL, AND TRIAL OVERSIGHT CONSIDERATIONS

10.1 Local Regulations/Declaration of Helsinki

This trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH Tripartite Guideline for GCP and the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

10.2 Ethical Review

It is the understanding of the sponsor that this protocol (and any amendments) as well as appropriate consent procedures, will be reviewed and approved by a research ethics board (REB)/ institutional review board (IRB). This board must operate in accordance with the current federal regulations. For sites with a local ethics committee, a letter or certification of approval will be sent by the investigator to the sponsor (or contract research organization [CRO]) before initiation of the trial and also whenever subsequent modifications to the protocol are made.

10.3 Informed Consent Process

An ICF describing in detail the trial treatment, trial procedures, and risks will be given to the participant, along with an assent form when required.

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulation), to obtain written informed consent from each individual participating in this trial, after adequate explanation of the aims, methods, objectives, and potential hazards of the trial.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the trial and continues throughout the individual's trial participation. Consent forms will be IRB/REB approved, and the participant will be asked to read and review the document. The investigator will explain the research trial to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the trial and of his or her rights as a research participant. 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 trial with their family or surrogates or think about it prior to agreeing to participate.

The participant will sign the informed consent document prior to any procedures being done specifically for the trial. Participants must be informed that participation is voluntary and that they may withdraw from the trial at any time for any reason, without prejudice. A copy of the signed informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any trial-specific procedures.

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 trial.

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/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 trial.

10.4 Trial Discontinuation and Closure

This trial may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for trial suspension or termination, will be provided by the suspending or terminating party to trial participants, investigators, the sponsor, and regulatory authorities. If the trial is prematurely terminated or suspended, the principal investigators will promptly inform trial participants and the IRB/REB, and will provide the reason(s) for the termination or suspension. Trial participants will be contacted, as applicable, and be informed of changes to trial visit schedule.

Circumstances that may warrant termination or suspension of the trial include, but are not limited to the following:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete or evaluable
- Scientific or corporate reasons

The trial may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, IRB/REB, Health Canada, and/or FDA.

10.5 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the trial protocol, documentation, data, and all other information generated will be held in strict confidence.

The investigator must assure that the participants' anonymity will be maintained and that participants' identities are protected from unauthorized parties. On case report form (CRF) or other documents submitted to the sponsor, participants should not be identified by their names, but by an identification code. The investigator should keep a participant log relating codes with the names of participants. The investigator should maintain in strict confidence documents not for submission to Horizon Therapeutics Ireland DAC (e.g., participants' written consent forms).

All research activities will be conducted in a setting as private as possible.

The trial monitor, other authorized representatives of the sponsor, and representatives of the IRB,

regulatory agencies, or pharmaceutical company supplying IP may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this trial. The clinical trial site will permit access to such records.

The trial participant's contact information will be securely stored at each clinical site for internal use during the trial. At the end of the trial, all records will continue to be kept in a secure location for as long a period as dictated by the applicable legal or regulatory requirements, the reviewing IRB, institutional policies, or sponsor requirements.

10.6 Clinical Monitoring

Clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected; that the reported trial data are accurate, complete, and verifiable; and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), ICH GCP guidelines, and with applicable regulatory requirement(s). Centralized monitoring, which consists of remote review of accumulating data from all sites, will be performed as detailed in the Centralized Monitoring Plan.

10.7 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of trial conduct, data and biological specimen collection, documentation, and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system, and data QC checks, which will be run on the database, will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

During the trial, the sponsor or its representative will conduct monitoring visits at regular intervals. The monitoring visits will be conducted to ensure protocol adherence, quality of data, accuracy of entries on the eCRFs, IP accountability, compliance with regulatory requirements, and continued adequacy of the trial site and its facilities.

The site may be audited, monitored, or inspected by a quality assurance officer named by the sponsor, by the REB or IRB, and/or by the regulatory authorities. The investigator will be given notice before an audit occurs and will be expected to cooperate with any audit and provide assistance and documentation (including source data) as requested. The trial site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities.

10.8 Data Handling and Record Keeping

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

The investigator must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. These documents should be classified into two separate categories: investigator's study files and participant clinical source documents.

The investigator must maintain source documents for each participant in the trial. These 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. All information on the eCRFs must be traceable to the source documents in the participant's file. Data not requiring a written or electronic record will be defined before trial start and will be recorded directly on the eCRFs, which will be documented as being the source data.

The records should be retained by the investigator according to ICH guidelines, local regulations, or as specified in the Clinical Trial Agreement, whichever retention period is longer.

Participant data will be entered by site personnel using Medidata Rave, a web-based electronic data capture (EDC) and reporting system. This application will be set up for remote entry. Medidata is the developer and owner of Rave EDC. The EDC software has been fully validated and conforms to Title 21 of the Code of Federal Regulations, Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been fully trained. Designated investigator staff will enter the data required by the protocol into the eCRFs using this web-based application. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the investigator staff before confirming the data. The investigator must certify that the data are complete and accurate by applying an electronic signature to the eCRFs.

The data collected will be encoded and stored electronically in a database system. Validated data may subsequently be transferred to the sponsor.

10.9 Biological Specimens and Data

Study data are protected by the use of a sample identification (SID) 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 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 data or samples will be collected unless specifically required to monitor the safety of the participant.

Leftover samples stored for future research with participant consent will be labeled with a sample identification number. If the participant consents to have his/her 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 sample(s) 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 his/her 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. If future use consent is withdrawn, the Sponsor and the investigator will ensure that the participant's sample(s) are destroyed unless the identification number has been

removed and the participant can no longer be linked to any samples. 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.

10.10 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The non-compliance may be either on the part of the participant, the investigator, or the trial site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. The CRA must ensure that a prompt action is taken to secure compliance. If a non-compliance that significantly affects or has the potential to significantly affect human participant protection or reliability of trial results is discovered, the CRO and the Sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions

Protocol deviations must be sent to the reviewing IRB per their policies. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.11 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 trial will be registered on ClinicalTrials.Gov prior to the first participant being dosed.

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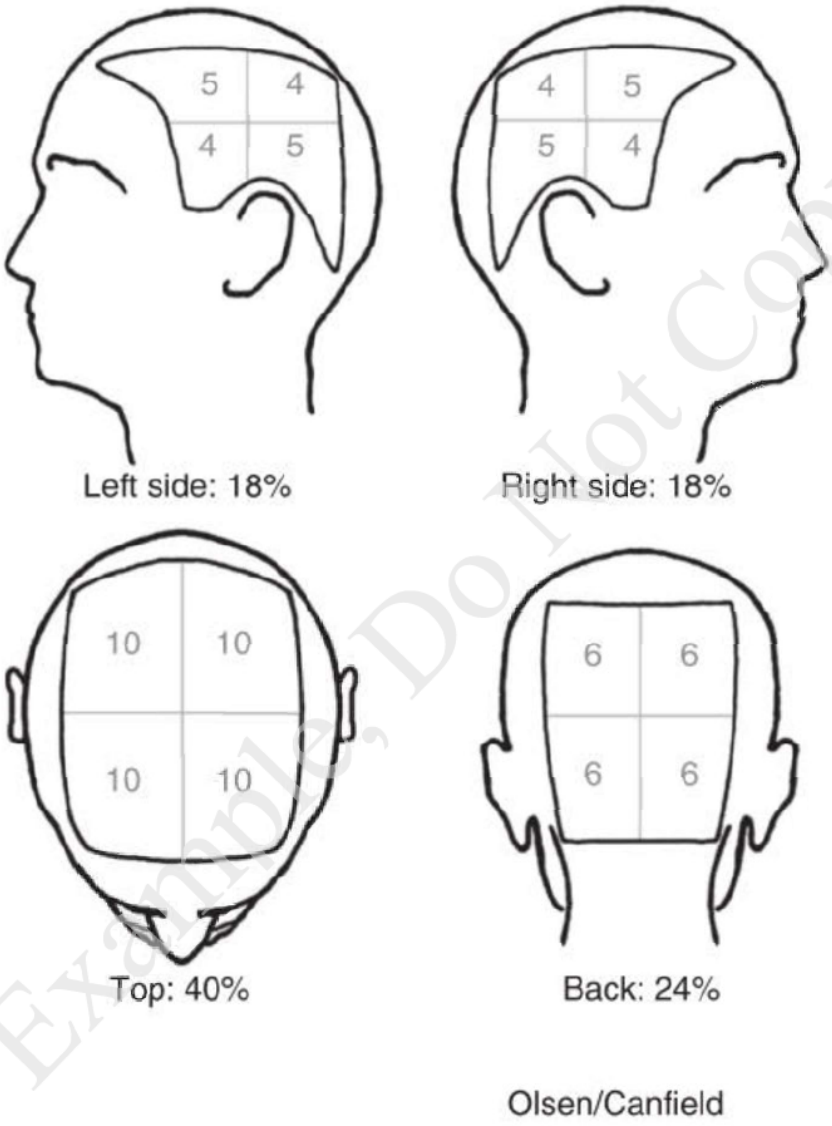
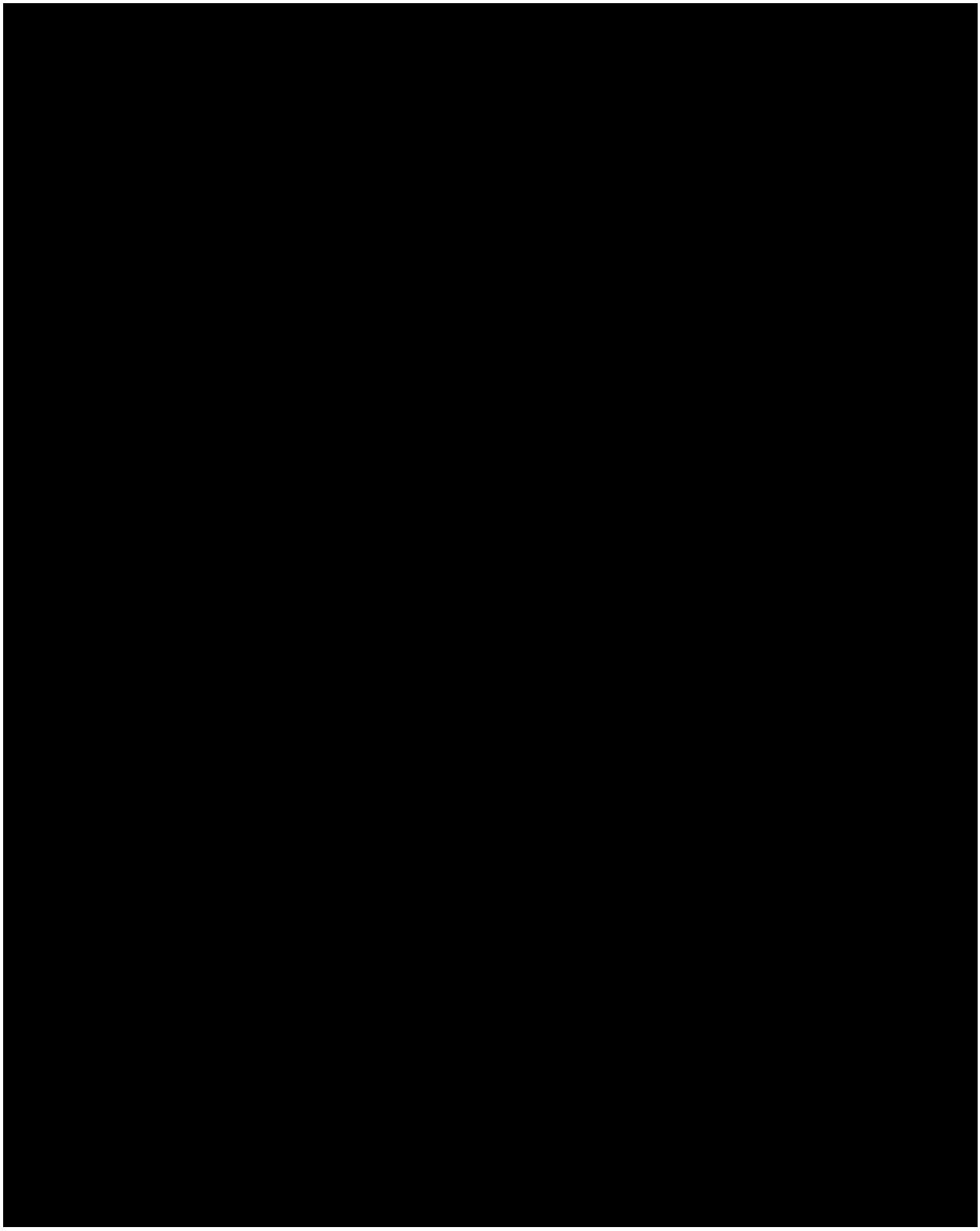
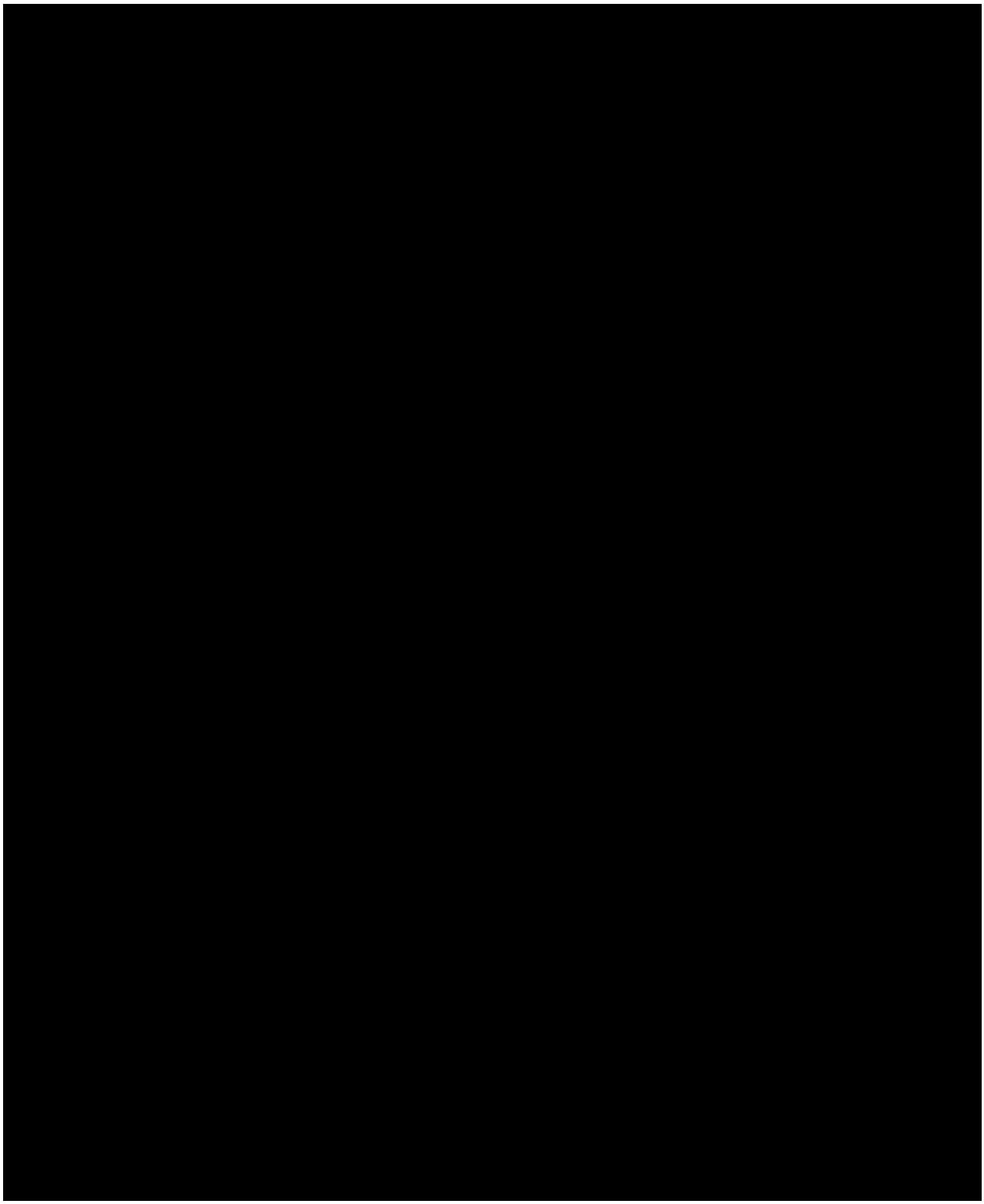
APPENDIX 1: Severity of Alopecia Tool (SALT)[21]



Olsen/Canfield

Left Quadrant Raw Score (LRS)		Top Quadrant Raw Score (TRS)	
Right Quadrant Raw Score (RRS)		Back Quadrant Raw Score (BRS)	
Total SALT Score [(LRS x 0.18) + (RRS x 0.18) + (TRS x 0.40) + (BRS x 0.24)]			





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Subject: Your electronic signature is required by Innovaderm Research-HZNP-DAX-201 Protocol Version 2.0_Final
Source Envelope:
Document Pages: 70
Signatures: 3
Certificate Pages: 5
Initials: 0
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Electronic Record and Signature Disclosure: Accepted: 07-Jan-2022 | 13:37 ID: 62dd39d6-4913-45f2-ac96-04cd0acb038b		
[redacted] Security Level: Email, Account Authentication (Required)	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 07-Jan-2022 | 13:07:27 CST 94348E43E05145848D3DCFDE0A20F5C3 Signature Adoption: Pre-selected Style Signature ID: 94348E43-E051-4584-8D3D-CFDE0A20F5C3 Using IP Address: 206.18.108.11 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 07-Jan-2022 | 13:38 Viewed: 07-Jan-2022 | 14:06 Signed: 07-Jan-2022 | 14:07
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Signer Events	Signature	Timestamp
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In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp
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Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
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Certified Delivered	Security Checked	07-Jan-2022 | 14:12
Signing Complete	Security Checked	07-Jan-2022 | 14:13
Completed	Security Checked	07-Jan-2022 | 14:13

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

Electronic Record and Signature Disclosure created on: 22-Nov-2016 | 16:31
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